X=Y–ZH Systems as Potential 1,3-Dipoles. Part 10.[1] The Decarboxylative Route to Azomethine Ylides. Background and Relevance to Pyridoxal Decarboxylases

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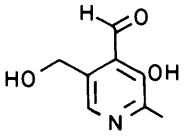
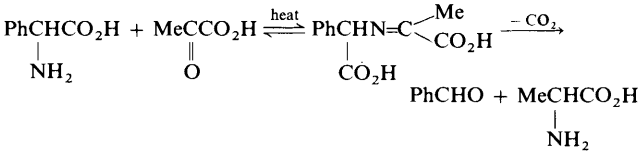
The reaction of primary and α,α-disubstituted α-amino acids with pyridoxal in the presence of *N*-phenylmaleimide in various solvents at temperatures up to 120 °C gives rise to two series of cycloadducts. One series arises from azomethine ylides formed by decarboxylation of the intermediate pyridoxal imines whilst the other series arises *via* azomethine ylides derived by 1,2-prototropy in the same pyridoxal imines. The relevance of the decarboxylative route to azomethine ylides to the Strecker degradation and to pyridoxal-mediated decarboxylase enzymes is discussed.

In 1862 Strecker[2] observed that alloxan reacts with alanine to form carbon dioxide and acetaldehyde. This degradation of α-amino acids on heating with carbonyl compounds to give aldehydes with one fewer carbon atom subsequently became known as the Strecker degradation.[3] It was some seventy years after Strecker's original observation that Franke[4] correctly proposed the involvement of an imine in this degradation. Later the discovery of the involvement of α-amino acid decarboxylases in the biosynthesis of a number of physiologically important amines such as γ-aminobutyric acid (GABA),[5] dopamine,[5] serotonin,[5] and histamine[6] focussed attention on the prosthetic groups of these enzymes. Decarboxylases employ specialised carbonyl compounds as the prosthetic group, usually pyridoxal (Vitamin B_6) (**1**), but several examples are known which employ pyruvate.[6]



(**1**)

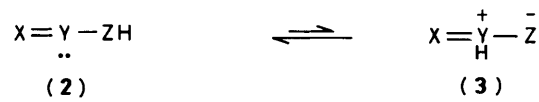
Model reactions mimicking the enzymatic decarboxylations were reported by several different groups. Thus Herbst and Engel[7] showed that phenylglycine reacts with pyruvic acid in boiling water to give benzaldehyde and alanine (Scheme 1) *via* imine formation.[8] In a series of papers Snell and co-workers[9] showed that pyridoxal reacted with α-amino acids in the presence of polyvalent metal cations to reproduce the pyridoxal enzymatic processes, including decarboxylation, *in vitro*. However, the *in vitro* reactions tended to reproduce several of the biochemical processes simultaneously, *i.e.* they were not reaction specific.



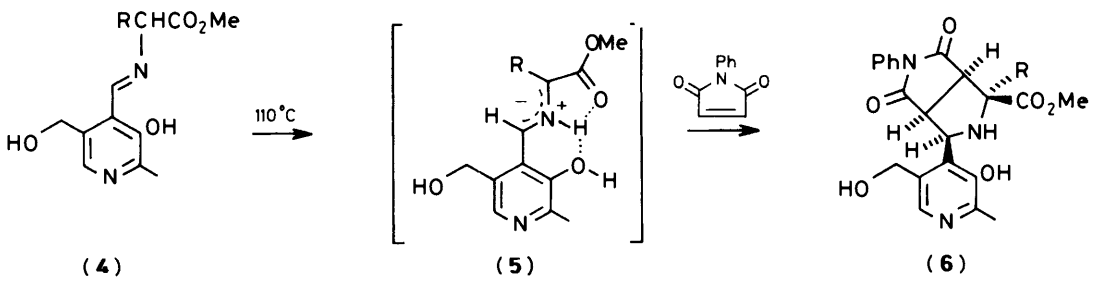
Scheme 1.

Scheme 1 became known as decarboxylative transamination and work on the enzymic processes and the Strecker degradation continued largely independently. The enzymic decarboxylations were later shown to proceed with retention of configuration.[10] Important contributions to the mechanism of the Strecker degradation were made by Chatelus[11] who showed that *N*-monosubstituted α-amino acids were substrates for the reaction. Schonberg and Moubacher's extensive studies[3] did much to delineate the scope of the Strecker degradation with respect to the carbonyl component, and Baddar's analysis of the reaction in terms of early electronic theory[12] was seminal.

Our interest in both the Strecker degradation and decarboxylative transamination arose from studies of our new general route to 1,3-dipoles involving 1,2-prototropy in X=Y–ZH systems (**2**) ⇌ (**3**).[13] The success of this new concept in generating 1,3-dipoles from imines,[14] hydrazones,[15] and oximes[16] led us to consider the possible relevance of such prototropy in biochemical processes mediated by pyridoxal enzymes.[14,17] We subsequently showed[17] that pyridoxal imines of α-amino acid esters undergo stereospecific cycloaddition



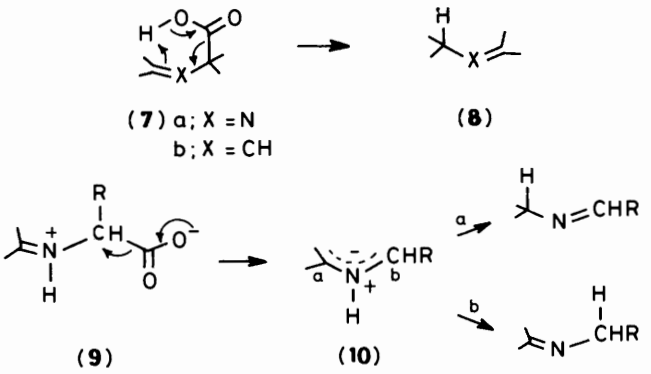
(**2**) (**3**)



(**4**) (**5**) (**6**)

(**4**) → (**6**) to *N*-phenylmaleimide *via* only one configuration (**5**) of the intermediate dipole.*

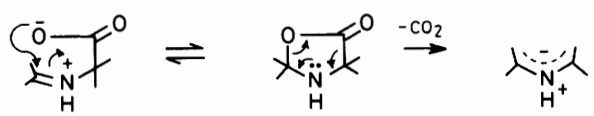
The success of the prototropic route to azomethine ylides led us to consider the possible involvement of azomethine ylides in the Strecker degradation and in decarboxylative transamination.[18] At this time the generally accepted mechanism (**7a**) → (**8a**)[19] for these processes was analogous to that established for β,γ-unsaturated acids (**7b**) → (**8b**).[20] This mechanism appeared unlikely to us since, based on a simple consideration of the pK_as of carboxylic acids ($pK_a \sim 4.5$) and protonated imines ($pK_a \sim 5.5$—6.5)[21] the imine (**7a**) should exist largely in the zwitterionic form (**9**). Decarboxylation of this latter species should then lead initially to a 1,3-dipole. The 1,3-dipole would then be expected to undergo a kinetically controlled proton transfer from nitrogen to carbon (**10**; a or b) depending on the electron density at these carbon sites (Scheme 2), generating



Scheme 2.

imine products which in the presence of water hydrolyse to amine and carbonyl compounds.

The published literature on the imine, amine, and carbonyl products from decarboxylative transamination appears to be readily interpretable in terms of this mechanism. Furthermore, the new mechanism is immediately open to a rigorous test by experiments designed to trap the postulated 1,3-dipole intermediate (**10**). Trapping experiments with a wide range of dipolarophiles were immediately successful[18] and gave rise to cycloadducts in good to excellent yield. Thus new powerful methodology for the generation of azomethine ylides was to hand. Our initial studies[18] led us to comment that dipole production *via* (**9**) → (**10**) (Scheme 2) might be expected to occur with little stereoselectivity. However, we have subsequently had occasion to modify the original Scheme (Scheme 2) since careful study of the stereochemistry of the azomethine ylides generated from carbonyl compounds and α-amino acids shows these processes occur stereospecifically or with high stereoselectivity and provides strong evidence for the intervention of an oxazolidin-5-one which generates the azomethine ylide by a stereospecific 1,3-dipolar cycloreversion (Scheme 3).[22,23]

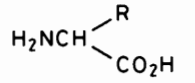


Scheme 3.

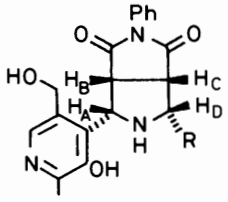
* A number of alternative structures are possible for the intermediate azomethine ylide (**5**) in which, for example, the pyridine nitrogen atom is protonated and/or the phenolic hydroxy group is deprotonated. We have no evidence that would enable us to distinguish between these possibilities.

Recently we became aware that Rizzi had previously suggested an azomethine ylide intermediate in the aldehyde-induced decarboxylation of *N-alkyl*amino acids under forcing conditions.[24] Fortunately for us he did not appreciate the scope and synthetic potential of the process which will tolerate wide variations in the carbonyl (formaldehyde, aliphatic, and aromatic aldehydes, aliphatic and aromatic ketones) and dipolarophile components, and occurs with all types of α-amino acids (primary, secondary; α,α-disubstituted; cyclic and acyclic) except tertiary α-amino acids.[18,22,23] Intramolecular cycloadditions to non-activated dipolarophiles can be readily achieved and provide an efficient route to multiply fused ring systems.[18] This aspect of the reaction has subsequently been used by others in natural product synthesis.[25]

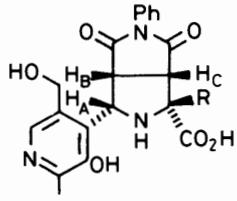
The stereochemistry, mechanism, and synthetic scope of the decarboxylative route to azomethine ylides will be the subject of subsequent papers in this series. The ability of pyridoxal (**1**) to function as the carbonyl component in the *in vitro* decarboxylation of α-amino acids *via* azomethine ylide formation is now considered.



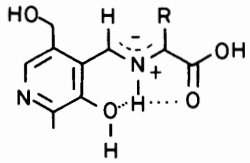
(**11**) a; R = Ph
b; R = CH_2OH
c; R = Me
d; R = CH_2Ph



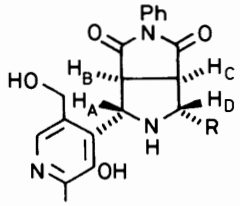
(**12**) a; R = Ph
b; R = H_E



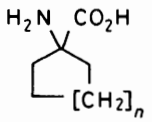
(**13**) a; R = H_D
b; R = CH_2OH
c; R = Me
d; R = CH_2Ph



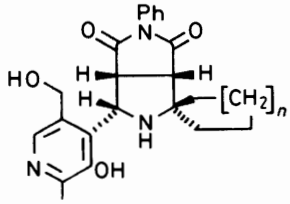
(**14**) a; R = H
b; R = CH_2OH
c; R = Me
d; R = CH_2Ph



(**15**) a; R = CO_2H
b; R = H



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



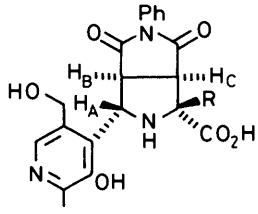
(**17**) a; n = 1
b; n = 2

When a mixture of pyridoxal (**1**), (**11a**), and *N*-phenylmaleimide was heated in boiling aqueous methanol for 4 h, a single cycloadduct (**12a**) was obtained in 70% yield. The stereochemistry of (**12a**), and of all the cycloadducts described in this paper, was established by n.O.e. difference spectroscopy. Thus irradiation of H_C effected enhancement of the signals for H_D (14%) and H_B (13%), whilst irradiation of H_B caused an 11% enhancement of the signals of both H_A and H_C. Repeating the reaction with glycine in place of (**11a**) gave, after 2 h, a 1:3.1 mixture of decarboxylated and undecarboxylated cycloadducts in 76% combined yield. The major (undecarboxylated) product arising from the prototropically generated dipole (**14a**) consists of a 3:1 mixture of *endo*-(**13a**) and *exo*-(**15a**) cycloadducts. We have previously reported the trapping of species analogous to (**14**)* in the racemisation of α-amino acids in the presence of aldehydes.[14,26] The minor (decarboxylated) product consists of a 1:1 mixture of *endo*-(**12b**) and *exo*-(**15b**) cycloadducts. Only the major isomer (**13a**) was isolated. The structural assignments of the other products were made on the basis of a 400 MHz ^1H n.m.r. spectrum of the mixture. The α,α-disubstituted α-amino acids (**16a,b**) react with pyridoxal and *N*-phenylmaleimide in boiling aqueous acetonitrile over 3 h to give the spiro adducts (**17a,b**) in 70% yield *via* an *endo* transition state. None of the product arising from an *exo* transition state was detected.

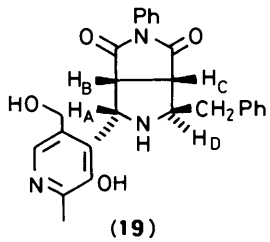
In contrast to the foregoing examples serine (**11b**) and alanine (**11c**) react with pyridoxal and *N*-phenylmaleimide in boiling aqueous methanol or boiling aqueous acetonitrile respectively to give solely or predominantly cycloadducts without decarboxylation, *i.e. via* the prototropically generated azomethine ylides (**14b,c**). Thus serine gives a single cycloadduct (**13b**) in 40% yield, whilst alanine gives (80%) a 9.7:1:1:0.5 mixture of (**13c**), (**18a**), and two minor decarboxylated cycloadducts. These latter cycloadducts could not be isolated in pure form and were not studied further. Phenylalanine (**11d**) similarly gives (boiling aqueous acetonitrile; 15 min) mainly cycloadducts arising from the prototropically generated dipole (**14d**) together with a minor amount of cycloadduct derived by the decarboxylative route. Thus a 3:2.1:1 mixture of (**13d**), (**18b**), and (**19**) is formed in 74% yield.

The stereochemistry of (**19**) was not firmly established but is assigned based on extensive stereochemical studies in related systems.[22]

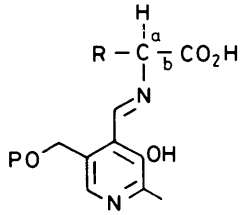
Pyridoxal phosphate-dependant enzymes occur widely and are responsible for the synthesis, racemisation, degradation, and interconversion of α-amino acids in living systems.[10,27] The reactive intermediates in these processes are generally believed to be generated by cleavage of either bond (a) or bond (b) in (**20**), together with protonation of the pyridine nitrogen atom giving (**21**) and (**22**) respectively. Stereoelectronic control requires that, for the direct conversion of (**20**) into (**21**) or (**22**), the breaking bond a or b in (**20**) be aligned with the pyridyl azomethine π-system.[28] In the case of decarboxylation (**20**) → (**22**) this presupposes the direct conversion of (**20**) into (**22**). However, the results reported in our preliminary communications[22,23] suggest the intervention of the oxazolidin-5-one (**24**) merits strong consideration as the key intermediate in pyridoxal enzyme-mediated decarboxylations. The cyclisation (**23**) ⇌ (**24**) is a 5-*endo-trig* process and although it has been proposed that such processes are not normally kinetically favoured [29] there are many examples of ready formal† 5-*endo-trig* cyclisation especially in imine systems.[30,31] The transition state for the 5-*endo-trig* cyclisation (**23**; arrows) has no stereoelectronic requirement for bond b to be coplanar with the



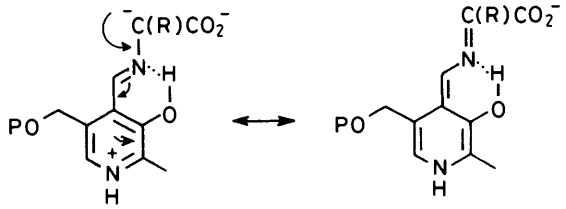
(**18**) a; R = Me
b; R = CH_2Ph



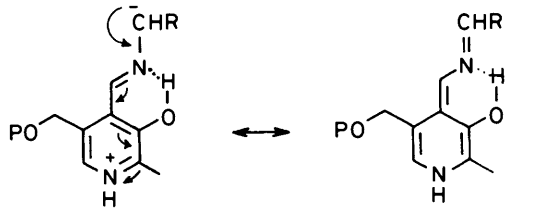
(**19**)



(**20**) $P = PO_3^{2-}$



(**21**)



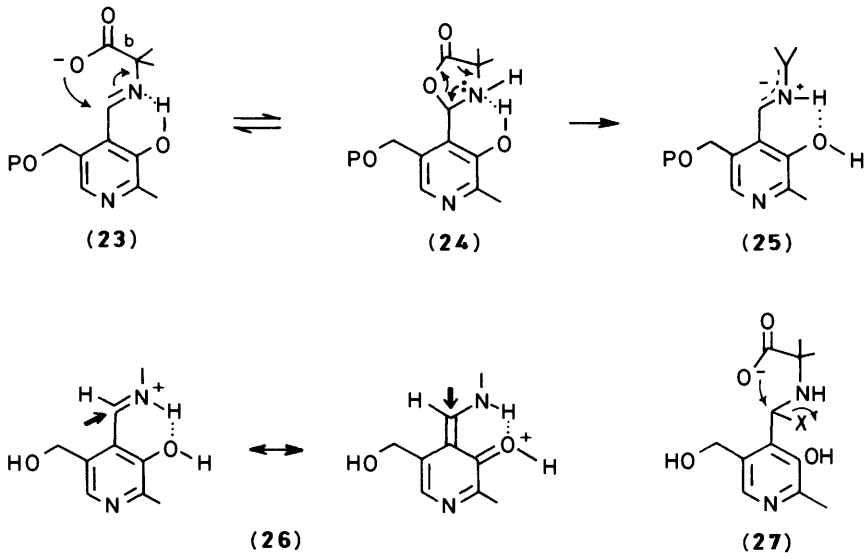
(**22**)

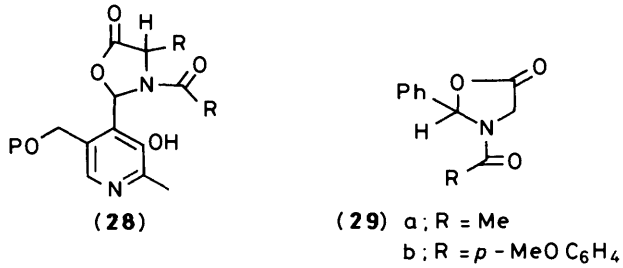
azomethine π-system, but the approach trajectory[32] of the carboxylate ion may well impose such planarity or near planarity. Any electron release from the pyridoxal ring will make the approach trajectory of the carboxylate ion geometrically more favourable (**26**). However, a 5-*exo-tet* process (**27**; arrows) whilst intuitively less likely cannot be ruled out. Loss of carbon dioxide with generation of the azomethine ylide then occurs by stereospecific 1,3-dipolar cycloreversion.[23] Surprisingly the suggestion of the possible involvement of an oxazolidin-5-one in processes mediated by pyridoxal enzymes is not entirely new. Thus Hiskey[33] suggested that the *N*-acylated oxazolidin-5-one (**28**) might be an intermediate in pyridoxal-mediated transamination processes. It was of interest therefore to see if such compounds decarboxylate to *N*-acyl azomethine ylides. When (**29a** or **b**) was heated at 180 °C for 2 h in iodobenzene in the presence of *N*-methylmaleimide no cycloadducts were observed and the *N*-acylated oxazolidin-5-ones (**29a** and **b**) were recovered unchanged. Presumably the lack of electron release from the amidic nitrogen atom retards the 1,3-dipolar cycloreversion.

The precise mechanism by which pyridoxal decarboxylases effect decarboxylation of α-amino acids has important implications for the design of suicide substrates of these enzymes. Our studies[22,23] suggest the 5-*endo-trig* cyclisation–cycloreversion

* See footnote on p. 950.

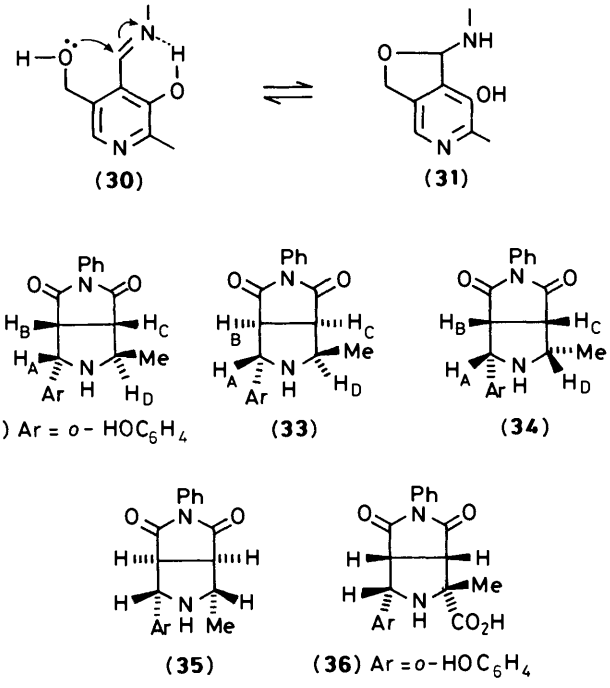
† Usually the data reported in the literature do not rule out alternative mechanisms of the non-5-*endo-trig* type.





Scheme 4.

sequence (**23**) ⇌ (**24**) → (**25**) has much to commend it. The formation of cycloadducts of both pyridoxal-derived azomethine ylides (**14**) and (**25**; P = H), in some cases, arises from competition between 1,2-prototropy (**14**) and cyclisation–decarboxylation (**25**; P = H) (Scheme 3).



We believe the predominance of cycloadducts derived from (**14**), the azomethine ylide generated by 1,2-prototropy, is due to the supression of the 5-*endo-trig* cyclisation (**20**) ⇌ (**24**) necessary for generation of the decarboxylated azomethine ylide, by the favoured 5-*exo-trig* cyclisation (**30**) ⇌(**31**). Some evidence for this suggestion is provided by the observation that alanine (**11c**) reacts with salicaldehyde and *N*-methylmaleimide[dimethylformamide (DMF); 140 °C; 0.5 h] to give a 3:3:1:1:1 mixture of cycloadducts (**32**)—(**36**) in 74% combined yield. The stereochemistry of products (**32**)—(**35**) is assigned on the basis of coupling constants and comparisons with the benzaldehyde isomers [(**32**)—(**35**); Ar = Ph] for which full n.O.e. data are available.[23] In contrast to the high-temperature reaction in DMF, when the process is repeated in boiling aqueous acetonitrile over 2 days the sole product (71%) is (**36**).

Experimental

General spectroscopic details were as previously noted [34] except that all n.m.r. spectra were determined for solutions in [$^2H_5$]pyridine except where otherwise noted. Light petroleum refers to that fraction boiling in the range (60—80 °C).

Cycloaddition of Pyridoxal with α-Amino Acids and N-Phenylmaleimide.—General procedure. A mixture of equimolar amounts (5 mmol) of pyridoxal hydrochloride, sodium acetate trihydrate, and the α-amino acid, together with a slight excess of *N*-phenylmaleimide (6 mmol) in aqueous methanol [MeOH (60 ml) and water (10 ml)] or aqueous acetonitrile [MeCN (50 ml) and water (10 ml)], was boiled under reflux for between 15 min and 16 h during which time the starting materials dissolved. After completion of the reaction the solvent was removed under reduced pressure and the residue was crystallised from the appropriate solvent.

4-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6,8-*dioxo*-2,7-*diphenyl*-3,7-*diazabicyclo*[3.3.0]*octane* (**12a**). The reaction was carried out in aqueous methanol for 4 h. The *product* (70%) crystallised as plates from methanol, m.p. 270—272 °C (Found: C, 69.75; H, 5.55; N, 9.7. $C_{25}H_{23}N_3O_4$ requires C, 69.90; H, 5.40; N, 9.80%); *m/z* (%) 429 (M^+, 11) 256 (*M* − *N*-phenylmaleimide, 4), 173 (29), 106 (91), 105 (78), and 77 (100); $\nu_{max.}$ 3 540, 3 420, 3 260, 1 770, and 1 705 cm^{-1}; δ 8.3 (s, 1 H, PyH), 7.53 (m, 10 H, ArH), 5.69 (d, 1 H, H_A), 4.97 (s, 2 H, CH_2O), 4.86 (d, 1 H, H_D), 4.41 (t, 1 H, H_B), 4.00 (t, 1 H, H_C), and 2.68 (s, 3 H, Me).

4-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane* (**12b**) *and* (**15b**) *and* 4-(3-*hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic acid* (**13a**) *and* (**15a**). The crude product (76%) was shown by 400 MHz n.m.r. spectroscopy to comprise a 4.6:1.5:1:1 mixture of compounds (**13a**), (**15a**), (**12b**), and (**15b**). Crystallisation of the mixture from methanol afforded the *acid* (**13a**) as plates, m.p. 271—273 °C (Found: C, 59.15; H, 4.9; N, 10.2. $C_{20}H_{19}N_3O_6$·0.5 H_2O requires C, 59.10; H, 4.95; N, 10.35%); *m/z* (%) 353 (*M* − 44, 0.5), 188 (5), 187 (19), 173 (12), 149 (30), 119 (13), 93 (69), 77 (15), and 44 (100); $\nu_{max.}$ 3 600—2 320br, 1 775, and 1 705 cm^{-1}; δ 8.28 (s, 1 H, PyH), 7.45 (m, 5 H, ArH), 5.76 (d, 1 H, H_A), 5.04 (d, 2 H, CH_2O), 4.72 (d, 1 H, H_D), 4.42 (t, 1 H, H_B), 4.32 (t, 1 H, H_C), and 2.63 (s, 3 H, Me); compound (**15a**) had δ 8.36 (s, 1 H, PyH), 7.6 (m, 5 H, ArH), 6.30 (d, 1 H, H_A), 5.15 and 5.10 (AB, 2 H, CH_2O), 4.99 (d, 1 H, H_D), 4.59 (t, 1 H, H_B), 4.53 (t, 1 H, H_C), and 2.80 (s, 3 H, Me); compound (**12b**) had δ 8.25 (s, 1 H, PyH), 7.60 (m, 5 H, ArH), 6.15 (d, 1 H, H_A), 5.24 (d, 1 H, H_E), 4.7 (t, 1 H, H_B), and 2.66 (s, 3 H, Me). H_C, H_D, and CH_2O signals were obscured by overlapping signals; compound (**15b**) had δ 8.21 (s, 1 H, PyH), 7.60 (m, 5 H, ArH), 5.62 (d, 1 H, H_A), 5.19 (d, 1 H, part of C-5 CH_2 AB system. The other half was obscured by other signals), 4.64 (t, 1 H, H_B), and 2.66 (s, 3 H, Me). The signals for CH_2O and H_C were obscured.

4′-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6′,8′-*dioxo*-7′-*phenylspiro*(*cyclopentane*-1,2′-[3′,7′]*diazabicyclo*-[3.3.0]*octane*) (**17a**).—The reaction was carried out in aqueous acetonitrile for 3 h. The acetonitrile was then removed under reduced pressure, and the residue was dissolved in chloroform (100 ml) and the solution was washed with water (2 × 100 ml). The chloroform layer was dried (Na_2SO_4) and evaporated. The residue was crystallised from chloroform–ether to afford the *product* (70%) as prisms, m.p. 220—221 °C (Found: C, 66.2; H, 6.05; N, 9.95. $C_{23}H_{25}N_3O_4$·0.5H_2O requires C, 66.35; H, 6.00; N, 10.10%); *m/z* (%) 407 (M^+, 100), 360 (47), 216 (51), 189 (50), and 77 (34); $\nu_{max.}$ 3 450, 3 250, 1 770, and 1 700 cm^{-1}; δ($CDCl_3$) 7.78 (s, 1 H, PyH), 7.30 (m, 5 H, ArH), 5.14 (d, 1 H, H_A), 4.58 (2 × d, 2 × 1 H, CH_2O), 4.01 (t, 1 H, H_A), 4.58 (2 × d, 2 × 1 H, CH_2O), 4.01 (t, 1 H, H_B), 3.20 (d, 1 H, H_C), 2.39 (s, 3 H, Me), and 2.19 (m, 8 H, $[CH_2]_4$).

4′-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6′,8′-*dioxo*-7′-*phenylspiro*(*cyclohexane*-1,2′-[3′,7′]*diazabicyclo*-[3.3.0]*octane*) (**17b**).—Prepared in an analogous manner to that described above. The *product* (70%) crystallised from chloroform–ether as prisms, m.p. 245—246 °C (Found: C, 68.6; H, 6.45; N, 9.7. $C_{24}H_{27}N_3O_4$ requires C, 68.40; H, 6.45; N, 9.95%); *m/z* (%) 421 (M^+, 4), 360 (5), 205 (38), 173 (100), 113 (82), 93 (92), 54 (27), and 31 (35); $\nu_{max.}$ 3 450, 3 260, 1 770, and 1 700 cm^{-1}; δ($CDCl_3$) 7.78 (s, 1 H, PyH), 7.30 (m, 5 H, ArH), 5.22 (d, 1 H, H_A), 4.60 (dd, 2 H, CH_2O), 4.02 (t, 1 H, H_B), 3.32 (d, 1 H, H_C), 2.39 (s, 3 H, Me), and 2.13 (m, 10 H, $[CH_2]_5$).

4-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-2-*hydroxymethyl*-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic Acid* (**13b**).—The reaction was carried out in boiling aqueous methanol for 16 h according to the general procedure. The *product* (40%) crystallised as plates from methanol, m.p. 228—230 °C (Found: C, 57.3; H, 5.35; N, 9.55. $C_{21}H_{21}N_3O_7$·MeOH requires C, 57.50; H, 5.50; N, 9.15%); *m/z* (%) 429 (*M* + 2, 0.5), 377 (3), 365 (11), 93 (100), 77 (27), and 44 (62); $\nu_{max.}$ 3 500—2 500br, 1 775, 1 720, and 1 710 cm^{-1}; δ 8.30 (s, 1 H, PyH), 7.44 (m, 5 H, ArH), 6.03 (d, 1 H, H_A), 4.97 (AB, 2 H, PyCH_2O), 4.85 and 4.38 (2 × d, 2 × 1 H, CH_2O), 4.63 (dd, 1 H, H_B), 4.09 (d, 1 H, H_C), and 2.70 (s, 3 H, Me). Irradiation of the signal H_B effects enhancements in the signals due to H_A (7%) and H_C (11%) whilst irradiation of H_A causes enhancement of the signal for H_B (14%).

4-(3-*Hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-2-*methyl*-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic Acid* (**13c**) *and* (**18a**).—The reaction was carried out in aqueous acetonitrile for 15 min according to the general procedure. The 400 MHz n.m.r. spectrum of the product (70%) showed it to comprise a 9.7:1:1:0.5 mixture of diastereoisomers (**13c**) and (**18a**) and two cycloadducts derived from a decarboxylatively generated azomethine ylide. Fractional crystallisation of the mixture afforded the *major isomer* (**13c**) as plates from methanol, m.p. 199—202 °C (Found: C, 59.9; H, 5.2; N, 9.7. $C_{21}H_{21}N_3O_6$·0.5H_2O requires C, 60.00; H, 5.30; N, 10.00%); *m/z* (%) 393 (*M* − H_2O, 21), 376 (34), 375 (12), 367 (2), 359 (61), 358 (84), 173 (10), 119 (30), 93 (100), 77 (83), and 44 (59); $\nu_{max.}$ 3 600—2 500br, 1 770, and 1 705 cm^{-1}; δ 8.31 (s, 1 H, PyH), 7.43 (m, 5 H, ArH), 6.04 (d, 1 H, H_A), 5.10 (AB, 2 H, CH_2O), 4.65 (t, 1 H, H_B), 4.04 (d, 1 H, H_C), 2.65 (s, 3 H, PyMe), and 2.01 (s, 3 H, Me). Irradiation of the signal for H_A effects enhancements in the signal for the pyridyl CH_2OH (7.5%) and in that for H_B (7.5%). Irradiation of H_C causes enhancement in the signal of H_B (7%), and irradiation of the pyrrolidinyl 2-Me group causes small enhancements in the signals for H_A(2.5%), H_B (4%), and H_C (3%).

Isomer (**18a**) was not isolated in pure form. Its structure was assigned on the basis of its n.m.r. spectrum admixed with (**13c**) and the other two minor isomers: δ 8.06 (s, 1 H, PyH), 7.15 (m, 5 H, ArH), 5.66 (d, 1 H, H_A), 4.78 (AB, 2 H, CH_2O), 4.49 (t, 1 H, H_B), 3.38 (d, 1 H, H_C), 2.40 (s, 3 H, Py*Me*), and 1.64 (s, 3 H, Me). It did not prove possible to separate the remaining two isomers chromatographically. They each give rise to a characteristic doublet (1 H) at δ 5.30 and 5.45 respectively.

2-*Benzyl*-4-(3-*hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic Acid* (**13d**) *and* (**18b**) *and* 2-*Benzyl*-4-(3-*hydroxy*-5-*hydroxymethyl*-2-*methylpyridin*-4-*yl*)-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane* (**19**).—The reaction was carried out in aqueous acetonitrile for 15 min according to the general procedure. The 400 MHz n.m.r. spectrum of the product (74%) showed it comprised a 3:2.14:1 mixture of compounds (**13d**), (**18b**), and (**19**). Fractional crystallisation of this mixture afforded the *major isomer* (**13d**) as plates from methanol, m.p. 271—273 °C (Found: C, 65.0; H, 5.2; N, 8.3. $C_{27}H_{25}N_3O_6$·0.5-H_2O requires C, 65.30; H, 5.30; N, 8.45%); *m/z* (%) 452 (*M* − OH − H_2O, 11), 451 (5), 360 (9), 278 (8), 187 (7), 173 (13), 119 (17), 91 (100), 77 (53), and 44 (49); $\nu_{max.}$ 3 500—2 300br, 3 310, 3 220, 1 770, 1 720, and 1 715—1 695br cm^{-1}; δ 8.06 (s, 1 H, PyH), 7.30 (m, 10 H, ArH), 5.89 (d, 1 H, H_A), 4.97 and 4.85 (2 × d, 2 × 1 H, CH_2O), 4.42 (dd, 1 H, H_B), 4.03 (d, 1 H, H_C), 3.90 and 3.34 (2 × d, 2 × 1 H, CH_2Ph), and 2.35 (s, 3 H, Me). Irradiation of H_A effects enhancements in the signals of the pyridyl CH_2OH (9%), H_B (17.5%), and CH_2Ph (9%). Interestingly the diastereotopic protons of the benzyl methylene group show clearly differentiable n.O.e. enhancements, *i.e.* one signal is enhanced by 2.5% and the other by 6.5%. Irradiation of the signal for H_C causes enhancement of the signals for H_B (9.5%) and CH_2Ph (total 4.5%).

The other cycloadducts (**18b**) and (**19**) were not obtained pure. Their structures were assigned on the basis of the n.m.r. spectrum of mixtures of all three isomers but containing only minor amounts of (**13d**).

Compound (**18b**) had δ 8.05 (s, 1 H, PyH), 7.25 (m, 10 H, ArH), 5.20 (d, 1 H, H_A), 4.77 and 4.72 (AB, 2 H, CH_2O), 4.10 (dd, 1 H, H_B), 3.61 and 3.52 (AB, 2 H, CH_2Ph), 3.56 (d, 1 H, H_C), and 2.42 (s, 3 H, Me); compound (**19**) had δ 8.06 (s, 1 H, PyH), 7.21 (m, 10 H, ArH), 5.77 (d, 1 H, H_A), 4.89 and 4.82 (AB, 2 H,

CH_2O), 4.35 (t, 1 H, H_B), 4.25 (t, 1 H, H_C), 3.64 (m, 1 H, H_D), 3.53 and 2.95 (AB, 2 H, CH_2Ph), and 2.39 (s, 3 H, Me).

3-*Acetyl*-2-*phenyloxazolidin*-5-*one* (**29a**) (*with J. Idle*).—Prepared according to Hiskey's method.[33] The product crystallised from carbon tetrachloride as needles, m.p. 98—101 °C (lit.,[33] 99.5—102 °C); *m/z* (%) 205 (M^+, 19), 162 (36), 118 (25), and 43 (100). The ^1H n.m.r. spectrum showed the presence of two isomers involving restricted rotation about the amide bond: δ($CDCl_3$) (major isomer) 7.47 (s, 5 H, ArH), 6.94 (s, 1 H, ArCHN), 4.30 (AB, 2 H, CH_2N), and 2.15 (s, 3 H, Me); δ(minor isomer) 7.47 (s, 5 H, ArH), 6.64 (s, 1 H, ArCHN), 4.55 and 4.18 (AB, 2 H, CH_2N), and 1.92 (s, 3 H, Me).

3-(p-*Methoxyphenyl*)-2-*phenyloxazolidin*-5-*one* (**29b**) (*with J. Idle*).—Prepared by adaptation of Hiskey's method.[33] The *product* (5%) crystallised from ethanol as pale yellow needles, m.p. 141—145 °C (Found: C, 68.8; H, 5.05; N, 4.5. $C_{17}H_{15}NO_4$ requires C, 68.65; H, 5.10; N, 4.70%); *m/z* (%) 297 (M^+, 7), 162 (3), and 135 (100); δ($CDCl_3$) 7.54 (d, 2 H, ArH), 7.46 (s, 5 H, ArH), 6.92 (d, 2 H, ArH), 4.35 (m, 2 H, CH_2N), and 3.85 (s, 4 H, MeO and ArCHN).

4-(o-*Hydroxyphenyl*)-2-*methyl*-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane* (**32**—**35**) *and* 4-(o-*Hydroxyphenyl*)-2-*methyl*-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic Acid* (**36**).—A mixture of salicaldehyde (1.22 g, 10 mmol), alanine (890 mg, 10 mmol), and *N*-phenylmaleimide (1.73 g, 10 mmol) in DMF (50 ml) was heated at 140 °C for 0.5 h. The solvent was then removed under reduced pressure and the residue was triturated with chloroform (50 ml). Cycloadduct (**36**) (300 mg, 8%) was insoluble in chloroform and was removed by filtration, then crystallised from aqueous acetone to afford *prisms*, m.p. 250—252 °C (Found: C, 65.55; H, 4.95; N, 7.8. $C_{20}H_{18}N_2O_5$ requires C, 65.55; H, 4.95; N, 7.65%); *m/z* (%) 366 (M^+, 3), 348 (9), 331 (6), 322 (32), 193 (37), 173 (100), 149 (19), 93 (41), and 77 (35); $\nu_{max.}$ 3 600—3 300br, 3 200—2 800br, 2 720, 2 540, 1 775, 1 710, and 1 645 cm^{-1}; δ 7.27 (m, 9 H, ArH), 5.35 (d, *J* 8.9 Hz, 1 H, H_A), 4.21 (t, 1 H, H_B), 3.88 (d, *J* 7.9 Hz, 1 H, H_C), and 1.97 (s, 3 H, Me).

The chloroform solution was washed with water (3 × 50 ml) and evaporated to dryness. The n.m.r. spectrum of the residue (2.11 g, 65.5%) showed it to comprise a 3:3:1:1 mixture of compounds (**32**)—(**35**). Flash chromatography (silica) with 4:1 v/v ether–toluene as eluant gave isomer (**35**) first, followed by (**33**), (**32**), and finally a mixture of (**32**) and (**34**). Isomer (**34**) was not isolated in pure form and its n.m.r. spectrum (below) was assigned from the n.m.r. spectrum of the mixture of isomers (**32**) and (**34**).

Compound (**32**) gave *prisms* from methylene dichloride–light petroleum, m.p. 244—246 °C (Found: C, 70.7; H, 5.6; N, 8.6. $C_{19}H_{18}N_2O_3$ requires C, 70.80; H, 5.65; N, 8.70%); *m/z* (%) 322 (M^+, 30), 149 (100), 107 (10), 77 (6), and 58 (11); δ($CDCl_3$) 7.15 (m, 11-H, ArH, NH, and OH), 4.89 (d, *J* 9.2 Hz, 1 H, H_A), 4.14 (q, *J* 6.7 Hz, 1 H, H_D), 3.50 (t, 1 H, H_B), 3.15 (d, *J* 8.5 Hz, 1 H, H_C), and 1.31 (d, 3 H, Me).

Compound (**33**) was an amorphous solid from methylene dichloride–petroleum, m.p. 133—135 °C; *m/z* (%) 322 (M^+, 40), 307 (4), 149 (100), 107 (11), 93 (9), 77 (11), and 58 (69); δ($CDCl_3$) 7.15 (m, 11 H, ArH, NH, and OH), 4.96 (d, *J* 2.3 Hz, 1 H, H_A), 3.81 (dd, *J* 2.6 and 8.3 Hz, 1 H, H_B), 3.68 (m, 1 H, H_D), 3.39 (t, 1 H, H_C), and 1.35 (d, 3 H, Me).

Compound (**34**) had δ($CDCl_3$) 7.12 (m, 11 H, ArH, NH, and OH), 4.52 (d, *J* 8.8 Hz, 1 H, H_A), 3.5 (m, 1 H, H_D), 3.42 (t, 1 H, H_B), 3.26 (t, 1 H, H_C), and 1.45 (d, 3 H, Me).

Compound (**35**) had δ($CDCl_3$) 7.18 (m, 11 H, ArH, NH, and OH), 4.48 (d, *J* 7.3 Hz, 1 H, H_A), 3.58 (dd, *J* 7.4 and 9.5 Hz, 1 H, H_B), 3.49 (m, 1 H, H_D), 3.19 (dd, *J* 8.1 and 9.5 Hz, 1 H, H_C), and 1.56 (d, 3 H, Me).

4-(o-*Hydroxyphenyl*)-2-*methyl*-6,8-*dioxo*-7-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic Acid* (**36**).—Prepared (71%) by the general method in aqueous acetonitrile with salicaldehyde replacing pyridoxal and omitting sodium acetate. The product was identical with that described above.

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