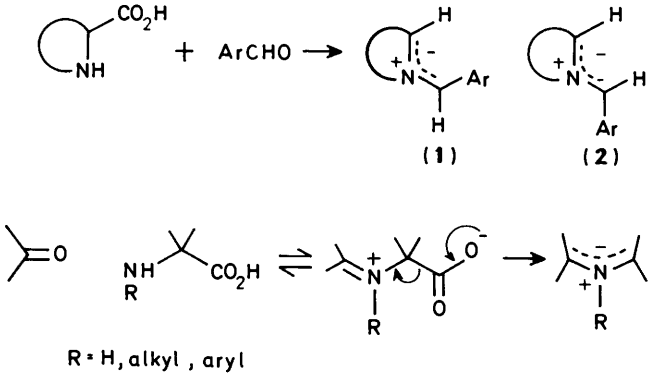
X=Y–ZH Systems as Potential 1,3-Dipoles. Part 12.[1] Mechanism of Formation of Azomethine Ylides *via* the Decarboxylative Route from α-Amino Acids

Ronald Grigg,* Jonathan Idle, Peter McMeekin, Sivagnanasundram Surendrakumar, and David Vipond
Department of Chemistry, Queen's University, Belfast BT9 5AG, Northern Ireland

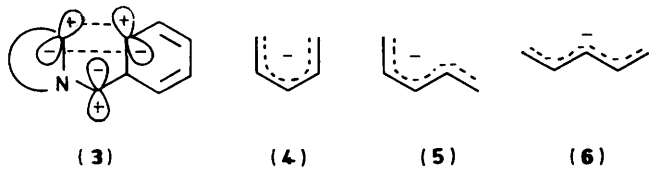
The effect of temperature, solvent, and type of aldehyde on the stereospecific or stereoselective formation of azomethine ylides by the decarboxylative condensation of aldehydes with three types of α-amino acids, (i) cyclic secondary α-amino acids, (ii) cyclic secondary α-amino acids with a benzylic carboxy group, and (iii) acyclic primary α-amino acids, has been studied. Stereospecific *anti*-dipole formation in (i) and temperature dependent stereoselective *anti*-dipole formation in (ii) and (iii) is inferred from the stereochemistry of cycloadducts of the azomethine ylides with *N*-methylmaleimide. These results are used to support a mechanistic scheme involving loss of carbon dioxide from intermediate oxazolidin-5-ones in a stereospecific cycloreversion reaction.

Our studies[2–4] of the stereochemistry of the cycloadducts produced from azomethine ylides generated from α-amino acids and carbonyl compounds *via* the decarboxylative route provided clear evidence of stereospecific formation of the *anti*-dipole e.g., (1) rather than the *syn*-dipole e.g., (2) in many instances, and lack of stereoselectivity in certain cases particularly where the carboxy group of the precursor α-amino acid was in a benzylic site.[1] The results necessitate reappraisal of our original simple scheme for azomethine ylide formation (Scheme 1) and require either the existence of a hitherto unrecognised non-covalent configuration-holding interaction or of an additional intermediate capable of exerting control over dipole stereochemistry.

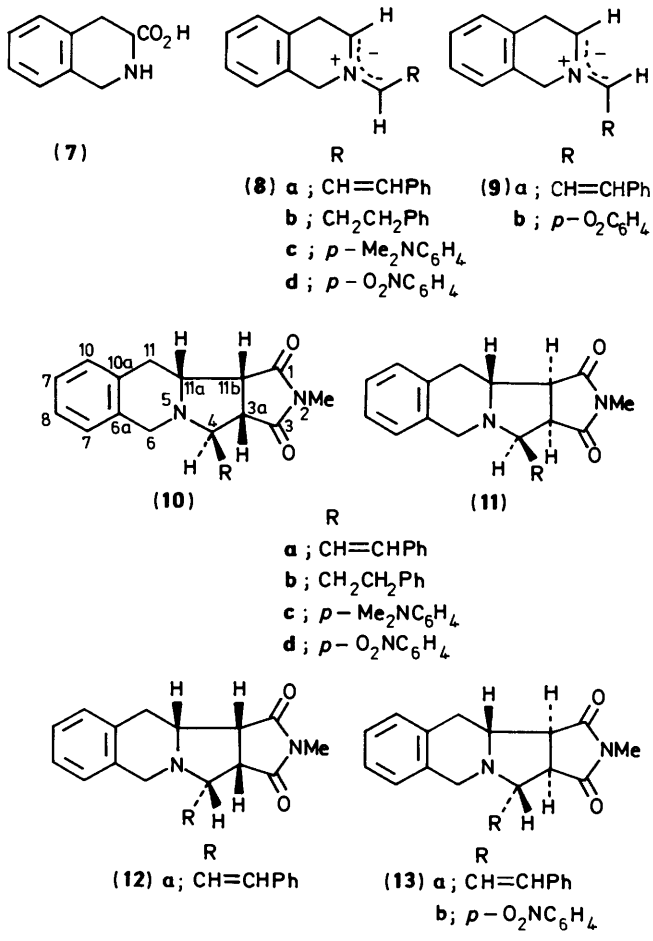


Scheme 1.

Cyclic Secondary α-Amino Acids.—A potential non-covalent configuration-holding interaction would be a 1,5-H.O.M.O. interaction (3) of the type possible in pentadienyl anions. Hoffmann and Olofson,[5] on the basis of M.O. calculations, proposed that such an interaction would be stabilising in pentadienyl anions resulting in a preference for the U-shaped anion (4) over the sickle- and W-shaped anions (5) and (6). However, Dewar's M.N.D.O. calculations favoured (6)[6] whilst

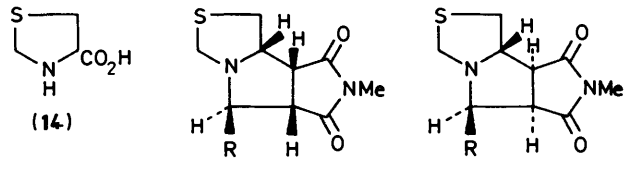


experimental results show the situation to be complex with both (4) and (6) being observed.[7] In the context of our decarboxylative route to dipoles such an interaction should favour *anti*-dipole (8a) formation from cinnamaldehyde and (7), whilst reaction of (7) with 3-phenylpropionaldehyde, which lacks the

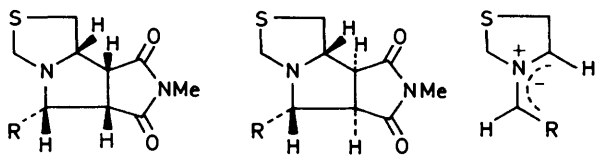


potential for 1,5-orbital interaction, should result in loss of dipole selectivity. *Precisely* the opposite result is observed. Thus compound (7) reacts with cinnamaldehyde and *N*-methylmaleimide in dimethylformamide (DMF) at 120 °C to give a

3:3:1.5:1 mixture of (**10a**)—(**13a**) derived from both *syn*- and *anti*-dipoles (**8a**) and (**9a**) respectively. Under similar conditions 3-phenylpropionaldehyde gives, *via* a stereospecifically generated *anti*-dipole (**8b**), a 1:1.5 mixture of isomers (**10b**) and (**11b**). Stereochemical assignments are made on the basis of n.O.e. difference spectroscopy (see Experimental section). A similar pattern was displayed by thiazolidine-4-carboxylic acid (**14**) which reacts (acetonitrile, 80 °C) with cinnamaldehyde and *N*-methylmaleimide to give a 2.03:1.11:1.96:1.0 mixture (78%) of (**15a**)—(**18a**) derived from both *anti*- and *syn*-dipoles, whilst under similar conditions 3-phenylpropionaldehyde gives a 1.5:1 mixture (73%) of (**15b**) and (**16b**) arising solely from the *anti*-dipole (**19**).



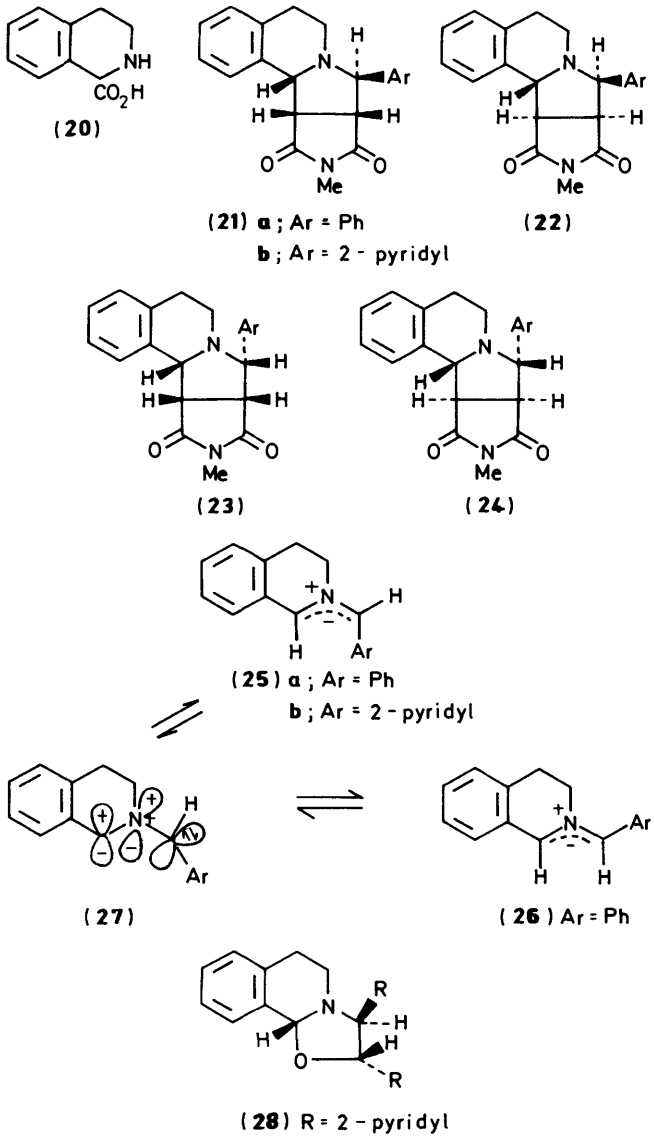
(**14**) (**15**) a; R = CH=CHPh; b; R = CH_2CH_2Ph (**16**)



(**17**) (**18**) (**19**)

Sensitivity to the aldehyde component is further evidenced by the reaction of (**7**) with *p*-dimethylaminobenzaldehyde and *N*-methylmaleimide (DMF, 120 °C, 10 h) which, although slow and incomplete, results in a 1:1.2 mixture (66%) of *endo*-(**10c**)- and *exo*-(**11c**)-cycloadducts arising solely from the *anti*-dipole (**8c**). When the reaction was repeated (DMF, 120 °C, 0.5 h) using *p*-nitrobenzaldehyde as the carbonyl component, the reaction was much faster and gave a 6:4:1 mixture (96%) of (**10d**), (**11d**), and (**13b**). The stereochemistry of the minor product (**13b**) was established as the *exo*-adduct of the *syn*-dipole (**9b**), by 2D COSY and ^1H NOEDSY. Thus in this latter case the cycloadducts reflect a 10:1 ratio of *anti*-(**8d**)- and *syn*-(**9b**)-dipoles.* Another feature of the cycloadducts arising from the *anti*-dipoles (**8c**) and (**8d**) is the effect of the *p*-substituent on the *endo*/*exo* ratios. Thus (**8c**) gives slightly more *exo*-adduct (**11c**) whilst (**8d**) gives rise to a 1.5:1 mixture of *endo*-(**10d**)- and *exo*-(**11d**)-adducts. The ability of *para*-substituents to affect the *endo*/*exo* cycloadduct ratio has been reported by us for a related case involving aryl imines of 2-aminomethylpyridines [8] and will be treated in more detail in a subsequent paper.

Cyclic Secondary α-Amino Acids with a Benzylic Carboxy Group.—A possible interpretation of the formation of *syn*-dipole when cinnamaldehyde and *p*-nitrobenzaldehyde are condensed with (**7**) or (**14**) is that stereospecific kinetic formation of the *anti*-dipole occurs followed by stereomutation, e.g. (**8**) ⇌ (**9**), promoted by the ability of R in (**8**) to delocalise negative charge. This suggestion would seemingly accord with the observation that tetrahydroisoquinoline-1-carboxylic acid



(**20**) (**21**) a; Ar = Ph, b; Ar = 2-pyridyl (**22**) (**23**) (**24**) (**25**) a; Ar = Ph, b; Ar = 2-pyridyl (**27**) (**26**) Ar = Ph (**28**) R = 2-pyridyl

(**20**), in which the carboxy group is in a benzylic site, reacts (DMF, 120 °C, 1 h) with benzaldehyde and *N*-methylmaleimide to give a 1.2:1.7:1.0:1.9 mixture of (**21a**)—(**24a**),[1] *i.e.*, a 1:1 ratio of adducts derived from *anti*-(**25a**)- and *syn*-(**26**)-dipoles. The same (incomplete) reaction at 21 °C (120 h) gives a 2.7:4.8:1.0:1.8 mixture of (**21a**)—(**24a**), *i.e.*, a 2.7:1 ratio of adducts derived from *anti*-(**25a**)- and *syn*-(**26**)-dipoles. Thus lowering the reaction temperature from 120 °C to 21 °C makes the reaction stereoselective and, incidentally, has a small effect on the *anti-exo*:*anti-endo* cycloadduct ratio which increases from 1.42:1 at 120 °C to 1.78:1 at 21 °C.

It is tempting to conclude that the latter increase in stereoselectivity for *anti*-dipole reflects the lower barrier to dipole stereomutation in (**25**) ⇌ (**26**) compared with (**8**) ⇌ (**9**) owing to the greater charge delocalisation, and consequent reduction in bond order in the dipole C–N–C moiety, afforded by the conjugation of two benzene rings to the dipole in the former case. Nevertheless, our previous work with azomethine ylides generated by 1,2-prototropy in imines of α-amino acids and their methyl esters [9] strongly suggested that dipole stereomutation was unlikely in the presence of such a reactive dipolarophile as *N*-methylmaleimide. Dipole stereomutation (**25**) ⇌ (**26**), *via* N–CHR bond rotation (**27**), if it occurred,

* This conclusion assumes the two dipoles react with *N*-methylmaleimide faster than they interconvert. Our previous studies [1,9] support this view but with less active dipolarophiles a different situation might obtain.

Table. Temperature dependence of cycloadduct ratio from reaction of (**29a**—**c**) with benzaldehyde and *N*-methylmaleimide in DMF

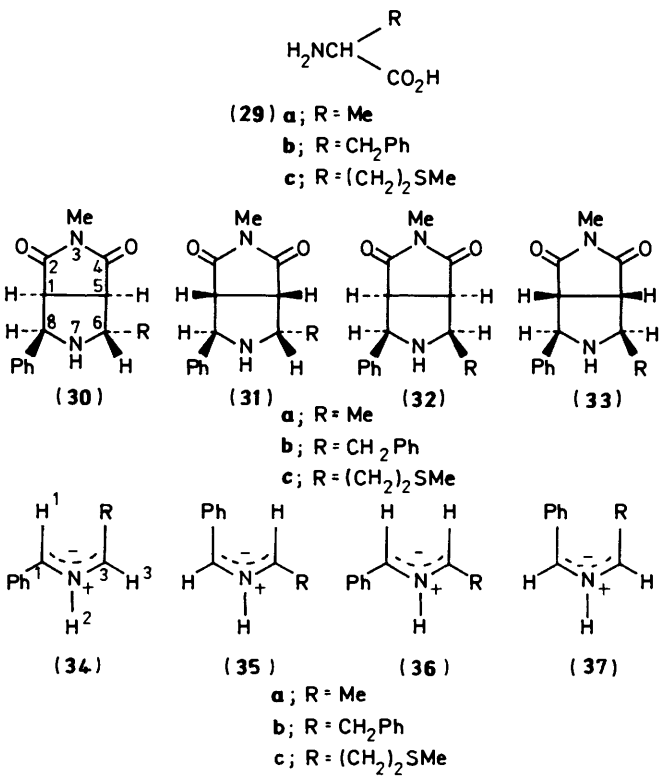
Substrate	Temp. (°C)	Cycloadduct ratio[a] (**30**)	(**31**)	(**32**)	(**33**)	*anti*:*syn*
	153	7.4	2.8	1.2	1	4.6:1
(**29a**)	120	8.6	4	1.3	1	5.5:1
	40	12.0	8.3	1	1	10.1:1
	153	4	1.3	1	1.1	2.5:1
(**29b**)	100	4.5	1.4	1.3	1	2.6:1
	60	5.4	2.4	1.8	1	2.8:1
	153	3.6	1.5	1	1	2.5:1
(**29c**)	100	5.0	2.3	1.1	1	3.5:1
	60	5.5	2.5	1.1	1	3.8:1

[a] All ratios calculated from peak areas in the 250 MHz ^{1}H n.m.r. spectra. For (**29a**) the C(Me) peaks were used. For (**29b**) the NMe peaks were used and for (**29c**) the signal for $-$PhC*H* was used.

would involve charge separation and should thus be sensitive to solvent polarity. However, there is little change in the *syn*:*anti* dipole adduct ratio in (**21a**)—(**24a**) when the cycloaddition is carried out in DMF (120 °C) (1:1 ratio) or in toluene (110 °C) (1.2:1 *anti*- to *syn*-ratio) suggesting dipole stereomutation is not occurring. The change in solvent/temperature does however affect the *exo*:*endo* cycloadduct ratio, which alters from 1.42:1 and 1.9:1 for *anti*- and *syn*-dipoles respectively at 120 °C in DMF to 1.88:1 and 3.1:1 in toluene at 110 °C. A definitive experiment was, however, needed to establish the stereochemical integrity of either the *anti*- or *syn*-dipole. This was provided by heating the oxazolidine (**28**), prepared *via* our iminium ion route to azomethine ylides,[10] in acetonitrile in the presence of *N*-methylmaleimide. The product consisted of a *ca.* 2.1:1 mixture of *endo*-(**21b**)- and *exo*-(**22b**)-cycloadducts derived *solely* from the *anti*-dipole (**25b**) together with pyridine-2-carbaldehyde. Thus, 1,3-dipolar cycloreversion of the oxazolidine (**28**) occurs stereospecifically, as expected,[11] to give the *anti*-dipole (**25b**) and the stereochemical integrity of (**25b**) is retained in the subsequent cycloaddition. In contrast when (**20**) is treated with pyridine-2-carbaldehyde and *N*-methylmaleimide in boiling acetonitrile (2.33 h) a 2.0:1.0:1.3:1.9 mixture of (**21b**)—(**24b**), arising from both *anti*- and *syn*-dipoles is obtained. When the same reaction is carried out in DMF at 120 °C the product consists of a 2.5:1.0:1.3:2.5 mixture of (**21b**)—(**24b**), showing little variation with the change in temperature and solvent.

Acyclic Primary α-Amino Acids.—Acyclic α-amino acids (**29a**—**c**) show a similar kinetic preference for the *anti*-dipole and the *anti*- to *syn*-dipole ratio is sensitive to temperature with lower temperatures favouring increased amounts of *anti*-dipole. Thus alanine (**29a**), benzaldehyde, and *N*-methylmaleimide react in DMF to give a mixture of four cycloadducts, two of which, (**30a**) and (**31a**) are derived from an *anti*-dipole and two of which, (**32a**) and (**33a**), are derived from a *syn*-dipole. As the reaction temperature is lowered from 153 °C to 40 °C the proportion of cycloadducts (**30a**) and (**31a**) derived from an *anti*-dipole increases (Table).

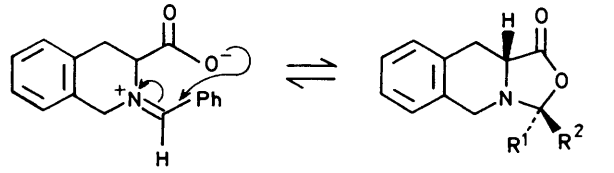
A similar trend to increased amounts of cycloadducts derived from an *anti*-dipole is shown by (**29c**) whilst (**29b**) shows only a small temperature dependence. In the acyclic amino acid case four dipole configurations are possible, two *anti*-dipoles (**34**) and (**35**), and two *syn*-dipoles (**36**) and (**37**). The stereochemistry of (**30a**—**c**)—(**33a**—**c**) was assigned on the basis of n.O.e. difference spectroscopy. Azomethine ylide (**34**) is sterically more favourable than (**35**) (R/H repulsion < Ph/H repulsion) suggesting that most, if not all, of (**30**) derives from (**34**) *via* an *endo*-transition state. Clearly the stereochemical anisotropy of the phenyl ring and hence its torsion angle with respect to the



C–NH–C dipole plane are important features of the transition states leading to dipoles (**34**)—(**37**). Note that if both *anti*-dipoles (**34**) and (**35**) were being produced in comparable amounts we might expect a decrease in the *endo*/*exo* cycloadduct ratio since the phenyl substituent is the only one capable of significant secondary orbital interaction. In fact the *anti*-dipole gives a better *endo*/*exo* ratio (Table) than the *syn*-dipole. In the latter case two configurations (**36**) and (**37**) are possible with (**36**) preferred over the sterically-congested (**37**). The steric effect of R (alkyl) in (**36**) seems to balance the secondary orbital effect of the phenyl substituent in the transition state since (**32**) and (**33**) are produced in approximately equal amounts (Table).*

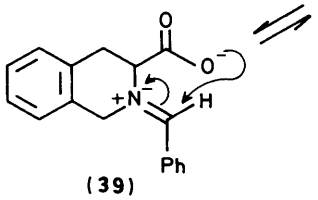
* The results of M.N.D.O. and STO-3G calculations on (**34a**)—(**37a**) and other aspects of dipole formation are being prepared for publication (R. Grigg, J. Idle, and P. McMeekin, unpublished observations).

Mechanism.—The kinetic preference for *anti*-dipole discussed previously[1] is thus confirmed, and sensitivity to temperature and structural features clearly demonstrated. However, the mechanistic basis for the observed kinetic preference for *anti*-dipole formation remains to be defined. With non-covalent orbital interactions effectively ruled out by our observations of cycloadduct stereochemistry from (**7**), *N*-methylmaleimide, and cinnamaldehyde or 3-phenylpropionaldehyde, we considered the possibility of an additional intermediate. The cyclisations



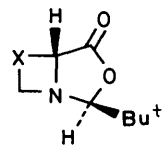
(**38**)

(**40**) **a**; R^1 = H, R^2 = Ph
b; R^1 = Ph, R^2 = H

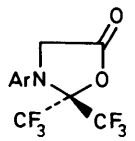


(**39**)

(**38**)→(**40**) and (**39**)→(**40**) could provide the necessary mechanistic control over dipole stereochemistry since (**40a**) and (**40b**) would be expected to undergo a stereospecific 1,3-cycloreversion[11] generating the *anti*- and *syn*-azomethine ylides (**8**; R = Ph) and (**9**; R = Ph) respectively. M.N.D.O. calculations on (**40a**) and (**40b**) show* that (**40a**) is more stable by 2.85 kcal mol^{-1}. Strong support for the involvement of oxazolidin-5-ones in the decarboxylative route to azomethine ylides is provided by the observation that proline and thiazolidine-4- and azetidine-2-carboxylic acids react stereospecifically with 2,2-dimethylpropionaldehyde to give a single oxazolidin-5-one (**41a**—**c**) respectively.[13] Moreover (**41a**) is reported to

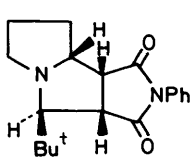


(**41**) **a**; X = $(CH_2)_2$
b; X = SCH_2
c; X = CH_2

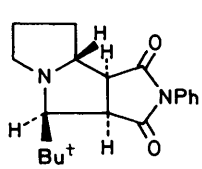


(**42**)

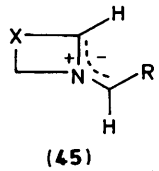
undergo cycloaddition (toluene, 105 °C, 16 h) to tetramethyl ethylene-1,1,2,2-tetracarboxylate with loss of carbon dioxide.[14] The oxazolidin-5-ones (**42**) also generate azomethine ylides on heating.[15] However, neither of these reports addressed the question of dipole stereochemistry. We therefore studied the reaction of (**41a**) with *N*-phenylmaleimide in boiling benzene. The reaction was slow† and progressed to *ca.* 65% conversion after 44 h at which time the product (> 90%) consisted of a 2.3:1 mixture of *endo*- and *exo*-cycloadducts (**43**) and (**44**) derived *solely* from the *anti*-dipole (**45a**). The stereochemistry of (**43**)



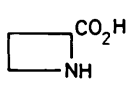
(**43**)



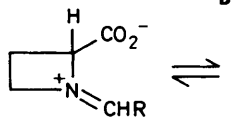
(**44**)



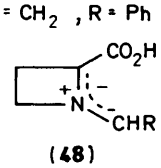
(**45**)
a; X = $(CH_2)_2$, R = Bu^t
b; X = CH_2, R = Ph



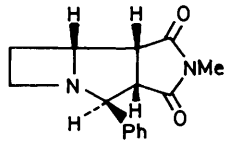
(**46**)



(**47**)



(**48**)



(**49**)

and (**44**) were assigned by 2D COSY and ^{1}H NOEDSY n.m.r. studies.

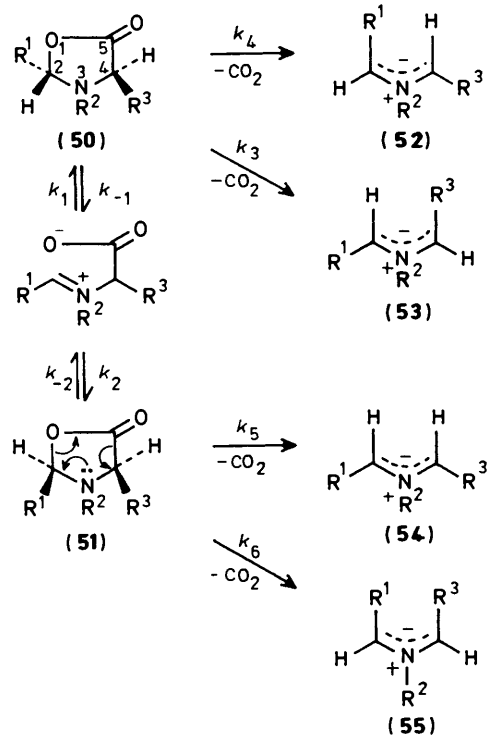
It is interesting to note that Seebach observed that when optically active proline and thiazolidine-4- and azetidine-2-carboxylic acids were used (hexane, 60 °C) to form (**41a**—**c**) only the latter case gave a racemic oxazolidin-5-one. Thus (**46**) generates the zwitterion (**47**) in which dipole formation (**48**), by deprotonation, competes effectively with cyclisation to (**41c**) in hexane at 60 °C. Cyclisation of (**47**) to (**41c**) is slower because it generates a more strained 4/5 fused ring system compared to the 5/5 fused ring systems (**41a**) and (**41b**) resulting from proline and thiazolidine-4-carboxylic acid. We have previously reported other systems where 1,2-prototropy competes with decarboxylation leading to azomethine ylides in which the carboxy group is retained or lost.[4] Interestingly compound (**46**) reacts with benzaldehyde and *N*-methylmaleimide (DMF, 120 °C) at about half the rate of the analogous reaction with proline to give a moderate yield (40%) of a single cycloadduct (**49**) derived from the *anti*-dipole (**45b**). Adducts in which the carboxy group is retained were not observed under these conditions.

Huisgen's extensive work on the cycloaddition reactions of mesoionic oxazolones (munchnones)[16] provides further numerous examples where transient bicyclic oxazolidin-5-ones undergo loss of carbon dioxide with concomitant formation of azomethine ylides. These intermediates can be isolated in certain bridged ring systems where decarboxylation is sterically disfavoured[17] or where the cycloreversion involves loss of carbonyl sulphide.[18] A series of spiro-oxazolidinones has been isolated from the reaction of ketenes with nitrones *via* an unusual rearrangement.[19] These spiro-oxazolidinones have been shown to undergo thermal cycloaddition to dimethyl acetylenedicarboxylate with loss of carbon dioxide.[20]

The results presented in this paper and in the preceding paper[1] provide strong support for the involvement of an oxazolidin-5-one intermediate in the decarboxylative route to azomethine ylides from both primary and secondary, cyclic and acyclic, α-amino acids. Our original simple scheme (Scheme 1) is thus modified to that shown in Scheme 2 in which the stereochemistry of the intermediate oxazolidin-5-one(s) determines the stereochemistry of the kinetically formed azomethine ylide(s).

The stereochemistry of the oxazolidin-5-ones is dependent on the steric and electronic effects of R^1—R^3 (Scheme 2), and their influence on the rate constants k_1, k_{-1}, k_2, k_{-2} and k_3—k_6 (Scheme 2) determines whether oxazolidinone formation is

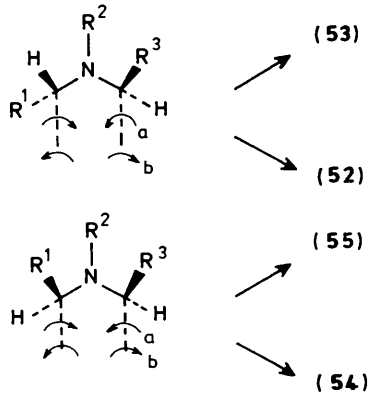
* See footnote on page 2705.
† A conveniently low temperature was chosen to suppress any tendency of (**41a**) to isomerise by ring-chain tautomerism.



Scheme 2.

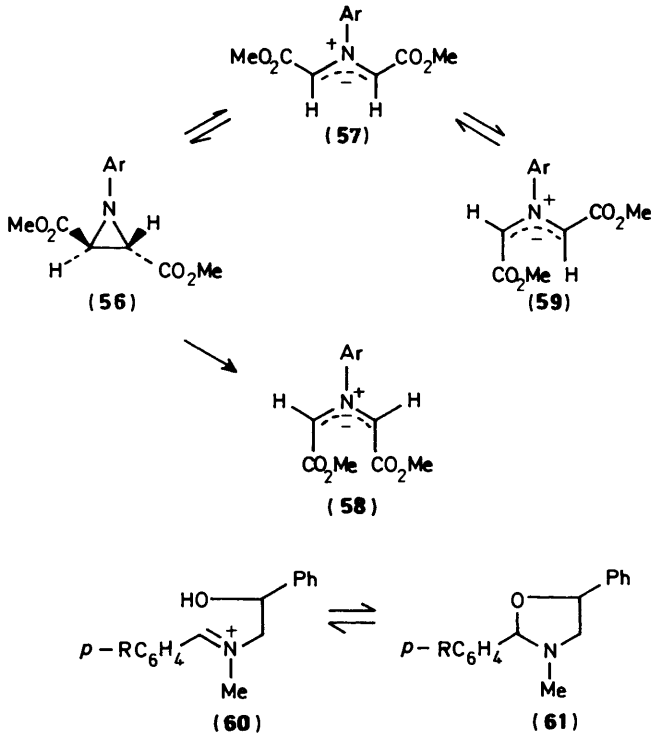
kinetically or thermodynamically controlled. Preferential generation of the *anti*-dipole could arise in two ways: (*a*) rate determining formation of the oxazolidinone, with the *trans*-oxazolidinone (**50**) kinetically favoured, followed by a fast stereospecific 1,3-cycloreversion of (**50**) to the *anti*-dipole, *i.e.*, $k_1 > k_2$ and k_3 and/or $k_4 > k_{-1}$ (Scheme 2); (*b*) fast equilibration of the oxazolidinones (**50**) and (**51**) (Scheme 2) followed by a rate determining stereospecific 1,3-cycloreversion with k_3 and/or $k_4 > k_5$ (Scheme 2).

Let us further consider the 1,3-cycloreversion step. In this process the sp^3 centres at C(2) and C(4) (Scheme 2) of the oxazolidin-5-ones (**50**) and (**51**) are rehybridising to sp^2 centres and the C(2) and C(4) centres are participating in a disrotatory twisting motion (Scheme 3) as the azomethine ylide is generated. In this process steric interactions between R^1, R^2, and R^3, and electronic interactions of R^1 and R^3 with the developing 1,3-dipole, manifest their influence over the two alternative disrotatory modes a and b available to both (**50**) and (**51**), and hence control the configurations of the *syn*- and *anti*-dipoles.



Scheme 3.*

The closest analogy to the interplay of rotational, steric, and electronic effects depicted schematically in Scheme 3 is provided by the thermal conrotatory opening of *trans*-2,3-disubstituted aziridines. Huisgen[21] has provided evidence that (**56**) opens to (**57**) and not (**58**) and has further shown[22] that $\Delta G^{\ddagger}$ for the stereomutation (**57**) ⇌ (**59**) is *ca.* 22 kcal mol^{-1}. Related kinetic studies showed that the azomethine ylides (**57**) and (**59**) have virtually the same energy but that (**59**) undergoes cycloaddition at a faster rate than (**57**).[23] This latter effect is ascribed to steric effects in the cycloaddition transition state.



In the context of our studies the cycloreversion of (**51**) to (**54**) rather than (**55**) seems secure based both on Huisgen's work and our unpublished STO-3G calculations† and assuming dipole stability is reflected in the cycloreversion transition state. Thus in the case of acyclic α-amino acids the *syn*-dipole produced is (**36**) and not (**37**). Cycloreversion of (**50**) to (**52**) or (**53**) would be expected to be more finely balanced and to depend on the nature of R^1, R^2, and R^3.

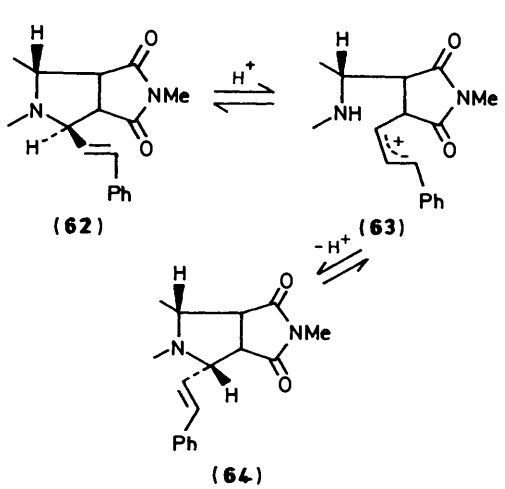
We have utilised three broad types of α-amino acids as azomethine ylide precursors in our studies. These are (i) cyclic secondary α-amino acids with a non-benzylic carboxy group which generate *anti*-dipole stereospecifically (with benzaldehyde as the carbonyl component), (ii) cyclic secondary α-amino acids with a benzylic carboxy group which generate azomethine ylides non-stereoselectively at 120 °C but show stereoselectively for *anti*-dipole at room temperature, and (iii) acyclic primary α-amino acids which are stereoselective for *anti*-dipole compared to *syn*-dipole by ≥2.5:1 at 153 °C and show increased selectivity as the temperature is lowered. The variation in stereoselectivity for *anti*-dipole with structure of the α-amino acid can be accommodated by Scheme 2 if there is a change in the rate determining step. Thus in case (i) which is exemplified by the reaction of (**7**) with 3-phenylpropionaldehyde to generate

* Simplified by omission of the –O–C(=O)– moiety.

† See footnote on page 2705.

the *anti*-dipole (**8b**) stereospecifically, cyclisation to the oxazolidin-5-one is fast and reversible with cycloreversion the rate determining step. There is evidence[24,25] of facile ring-chain equilibria in the related cyclisation of imines of β-aminoethanol derivatives to oxazolidines (**60**) ⇌ (**61**) at room temperature. This proposal requires that the oxazolidinone (**50**) undergoes a faster cycloreversion than (**51**). The precise reason for this is not obvious at present but is probably steric in origin (see below). Case (ii) is exemplified by the reaction of (**20**) with benzaldehyde. Non-stereoselective dipole formation might arise by a slow rate determining cyclisation of the zwitterion to (**50**) and (**51**) followed by a fast cycloreversion, *i.e.*, $k_3, k_4, k_5 > k_{-1}, k_{-2}$. This change in rate determining step is ascribed to the presence of two aryl rings at the termini of the developing dipole and their ability to delocalise the developing charge. Case (iii) which is exemplified by acyclic primary α-amino acids is probably analogous to case (i) except that in the rate determining cycloreversion step the difference between k_3 (or k_4) and k_5 (Scheme 2) is much less due to the reduced steric effects accruing in the cycloreversion transition state leading to (**54**) consequent on R^2 = H (Scheme 2).

The remaining results to be accommodated by Scheme 2 are the effects of variation of the aldehyde component in case (i). Thus 3-phenylpropionaldehyde, benzaldehyde, and *p*-dimethylaminobenzaldehyde react with (**7**) to give solely *anti*-dipole. In contrast, *p*-nitrobenzaldehyde and (**7**) give *ca.* 10% *syn*-dipole, and cinnamaldehyde and (**7**) react to give a 2.4:1 mixture of *anti*- and *syn*-dipoles. In the case of thiazolidine-4-carboxylic acid and cinnamaldehyde the *syn*-dipole predominates by 1.35:1. The small perturbation observed when *p*-nitrobenzaldehyde is used can be ascribed to the effect of the nitro group retarding the ring opening of the oxazolidin-5-ones (**50**) and (**51**), *i.e.*, decreasing k_{-1} and k_{-2}, due to the unfavourable resonance interaction of the iminium ion and the nitro group.† This would have the effect of slowing equilibration of (**50**) and (**51**) and hence introducing a small perturbation to the dipole stereochemistry. However, the formation of major amounts of *syn*-dipole when cinnamaldehyde is used as the aldehyde component doesn't fit this simple interpretation. The possibility of isomerisation after cycloaddition *via* ring-chain equilibrium, *e.g.*, (**62**) ⇌ (**63**) ⇌ (**64**), perhaps catalysed by a small amount of acid was disproved by a blank experiment. Thus (**16a**) was recovered unchanged after heating in acetonitrile at 80 °C for 22 h in the presence of 10 mol % benzoic acid.



(**62**) (**63**) (**64**)

† This would necessitate a concerted, but non-synchronous process, in which 1,2-bond cleavage is in advance of 4,5-bond cleavage.

It is possible that the styryl substituent on the oxazolidin-5-one ring has a similar effect to the benzylic carboxy group discussed in case (ii) in that it promotes a fast cycloreversion step, *i.e.*, cyclisation of the zwitterion to (**50**) and (**51**) (Scheme 2) either becomes rate determining or the two steps, cyclisation and cycloreversion, have comparable rates. Further work is in hand with substituted cinnamaldehydes to provide further data relevant to this suggestion.

The results described in this paper are, we believe, consistent with the trapping of kinetically formed dipoles by *N*-methylmaleimide. However, it is probable that dipole stereomutation will occur with azomethine ylides possessing aryl substituents at both termini if less active dipolarophiles are used.[9,27]

Experimental

General spectroscopic details were as previously noted.[26] Flash chromatography employed Silica Gel 60 (Merck 9385). Light petroleum refers to the fraction with b.p. 40—60 °C.

General Procedure for Decarboxylative Cycloaddition Reactions.—The carboxylic acid (0.01 mol), aldehyde (0.01 mol), and dipolarophile (0.01 mol) were stirred in DMF (50 ml) at 120 °C. When carbon dioxide gas evolution had ceased (or, in the case of sparingly soluble acids, when all the solids had dissolved), the reaction mixture was filtered, and the filtrate evaporated to dryness under reduced pressure. The resulting gum was dissolved in chloroform, and the solution washed with water (× 3), dried, and the solvent evaporated off to yield the crude product, usually as a mixture of isomers. Integration of the ^{1}H n.m.r. spectrum of the crude product gave, where applicable, the isomer ratio. Mixtures of isomers were separated using flash chromatography.

2,3,3a,4,6,11,11a,11b-*Octahydro*-2-*methyl*-4-(2-*phenylethenyl*)-1H-*pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-b]*isoquinoline*-1,3-*dione* (**10a**)—(**13a**).—Prepared from tetrahydroisoquinoline-3-carboxylic acid, cinnamaldehyde, and *N*-methylmaleimide using the general procedure. Heating at 120 °C was continued for 0.75 h. The crude isomer mixture was separated by flash chromatography eluting with 2:1 v/v toluene–ether to give (**10a**) (34%), (**12a**), and (**13a**) as a mixture of isomers (29%) and (**11a**) (33%) (combined yield 96%). Isomers (**12a**) and (**13a**) were separated by further flash chromatography eluting with 6:1 v/v benzene–ether.

2,3,3aα,4β,6,11,11aα,11bα-*Octahydro isomer* (**10a**). Colourless prisms (methanol), m.p. 209—212 °C (Found: C, 76.8; H, 6.1; N, 7.9. $C_{23}H_{22}N_2O_2$ requires C, 77.1; H, 6.2; N, 7.8%); $\nu_{max.}$ 1 760, 1 690 (amide), 755, 735, and 700 cm^{-1}; δ 2.67 (1 H, dd, *J* 11 and 16 Hz, 11α-H), 3.01 (3 H, s, 2-Me), 3.12 (1 H, dd, *J* 3.5 and 16 Hz, 11β-H), 3.20 (1 H, d, *J* 8 Hz, 3a-H), 3.38—3.44 (1 H, m, 11a-H), 3.56 (1 H, *J* 8 Hz, 11b-H), 3.89 (2 H, m, 6-H), 4.39 (1 H, d, *J* 10 Hz, 4-H), 6.23 (1 H, dd, *J* 10 and 16 Hz, olefinic-H), 6.77 (1 H, d, *J* 16 Hz, olefinic-H), and 6.97—7.41 (9 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 4-H caused enhancement of 3a-H (4) and olefinic doublet (10); irradiation of 11a-H caused enhancement of 11 β-H (5), 11b-H (8), and olefinic double doublet (8); irradiation of 11b-H caused enhancement of 3a-H (8) and 11a-H (3); *m/z* (%) 358 (M^+, 44), 267 (100), 247 (21), and 104 (55).

2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro isomer* (**11a**). Colourless rods (ethanol), m.p. 148—151 °C (Found: C, 76.9; H, 6.1; N, 7.9); $\nu_{max.}$ 1 765, 1 685 (amide), 745, and 695 cm^{-1}; δ 2.84 (2 H, m, 11-H), 3.05 (3 H, s, 2-Me), 3.11 (1 H, dd, *J* 1 and 8 Hz, 11b-H), 3.43 (1 H, t, *J* 8 Hz, 3a-H), 3.84 (1 H, t, *J* 8.5 Hz, 4-H), 3.86 (1 H, d, *J* 18 Hz, 6-H), 3.94 (1 H, ddd, *J* 1, 6, and 11 Hz, 11a-H), 4.06 (1 H, d, *J* 18 Hz, 6-H), 5.98 (1 H, dd, *J* 9 and 16 Hz, olefinic-H), 6.53 (1 H, d, *J* 16 Hz, olefinic-H), and 6.97—7.40 (9 H, m, ArH); ^{1}H

NOEDSY (%): irradiation of 3a-H caused enhancement of 4-H (8) and 11b-H (6); irradiation of 11a-H caused enhancement of 11b-H (2); irradiation of 11b-H caused enhancement of 3a-H (7) and 11a-H (3); *m/z* (%) 358 (M^+, 30), 267 (100), and 247 (10).

2,3,3aα,4α,6,11,11aα,11bα-*Octahydro isomer* (**12a**). Colourless platelets (ethanol), m.p. 238—240 °C (Found: C, 77.3; H, 6.1; N, 7.6); $\nu_{max.}$ 1 755, 1 680 (amide), 750, 740, and 690 cm^{-1}; δ 2.86 (1 H, m, 11a-H), 2.96—3.04 (1 H, m, 11β-H), 3.01 (3 H, s, 2-Me), 3.17 (1 H, dd, *J* 4 and 16 Hz, 11α-H), 3.24 (1 H, dd, *J* 7 and 9 Hz, 4-H), 3.27 (1 H, d, *J* 15 Hz, 6-H), 3.36—3.43 (2 H, m, 3a- and 11b-H), 4.07 (1 H, d, *J* 15 Hz, 6-H), 6.29 (1 H, dd, *J* 9 and 16 Hz, olefinic-H), 6.73 (1 H, d, *J* 16 Hz, olefinic-H), and 6.98—7.49 (9 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 11a-H caused enhancement of 4-H (5), 3a-H and 11b-H together (10), and 11α-H (7); *m/z* (%) 358 (M^+, 22), 267 (100), 247 (31), and 104 (37).

2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro isomer* (**11a**). Colourless rods (ethanol), m.p. 178—180 °C (Found: C, 76.9; H, 6.05; N, 7.8); $\nu_{max.}$ 1 755, 1 685 (amide), 745, and 690 cm^{-1}; δ 2.65 (1 H, m, 11a-H), 3.01 (3 H, s, 2-Me), 3.00 (1 H, m, 11α-H), 3.10 (1 H, t, *J* 8 Hz, 4-H), 3.18 (1 H, t, *J* 9 Hz, 11b-H), 3.29 (1 H, dd, *J* 8 and 9 Hz, 3a-H), 3.33—3.38 (2 H, m, 11β- and 6-H), 4.07 (1 H, d, *J* 15 Hz, 6-H), 6.26 (1 H, dd, *J* 8 and 16 Hz, olefinic-H), 6.76 (1 H, d, *J* 16 Hz, olefinic-H), and 7.00—7.46 (9 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 11a-H caused enhancement of 3a-H (0.5), 11b-H (2), and 4-H (5); irradiation of 11b-H caused enhancement of 11a-H (2); *m/z* (%) 358 (M^+, 29), 267 (100), 247 (20), and 104 (33).

2,3,3aα,4β,6,11,11aα,11bα *and* 2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro-2-methyl-4-(2-phenylethyl)-1H-pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-b]*isoquinoline-1,3-dione* (**10b**) *and* (**11b**).—Prepared from tetrahydroisoquinoline-1-carboxylic acid, 3-phenylpropionaldehyde, and *N*-methylmaleimide by the general method. Heating at 120 °C in DMF was continued for 3.5 h. The crude isomer mixture, the ^{1}H n.m.r. spectrum of which ($CDCl_3$) showed it to consist of a 1:1.5 mixture of (**10b**) and (**11b**), was separated by flash chromatography eluting with 15:1 v/v benzene–ethyl acetate to give (**10b**) (17%), (**11b**) (30%), and mixed fractions (17%) giving a combined yield of 64%.

Compound (**10b**). Colourless needles (ethanol), m.p. 145—147 °C (Found: C, 76.5; H, 6.6; N, 7.8. $C_{23}H_{24}N_2O_2$ requires C, 76.6; H, 6.7; N, 7.8%); $\nu_{max.}$ 1 760, 1 685 (amide), 750, and 703 cm^{-1}; δ 1.54 and 2.15 (2 × 1 H, 2 × m, CH_2), 2.60 (1 H, dd, *J* 11 and 16 Hz, 11β-H), 2.75 (2 H, m, $ArCH_2$), 2.98 (3 H, s, 2-Me), 3.05 (1 H, dd, *J* 4 and 16 Hz, 11α-H), 3.19 (1 H, d, *J* 8 Hz, 3a-H), 3.29 (1 H, ddd, 11a-H), 3.43 (1 H, t, *J* 8 Hz, 11b-H), 3.81 (1 H, dd *J* 3 and 11 Hz, 4-H), 3.86 (1 H, d, *J* 15 Hz, 6-H), 3.99 (1 H, d, *J* 15 Hz, 6-H), and 6.99—7.34 (9 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 3a-H caused enhancement of 4-H (3), 11b-H (6), both $ArCH_2$ (6), and CH_2 (3); irradiation of 11a-H caused enhancement of 11b-H (7) and CH_2 (5); *m/z* (%) 360 (M^+, 15), 255 (100), and 104 (12).

Compound (**11b**). Colourless rods (ethanol), m.p. 121—123 °C (Found: C, 76.5; H, 6.8; N, 7.7); $\nu_{max.}$ 1 770, 1 685 (amide), 750, 745, and 700 cm^{-1}; δ 1.69 (1 H, m, C*H*H), 1.99 (1 H, m, C*H*-H), 2.47 (1 H, m, $ArCH_2$), 2.76 (2 H, m, 11-H), 3.03 (3 H, s, 2-Me), 3.03 (1 H, d, *J* 8 Hz, 11b-H), 3.18 (2 H, m, 4-H and $ArCH_2$), 3.40 (1 H, t, *J* 8 Hz, 3a-H), 3.87 (1 H, d, *J* 18 Hz, 6-H), 3.92 (1 H, dd, *J* 7 and 11 Hz, 11a-H), 4.14 (1 H, d, *J* 18 Hz, 6-H), and 7.02—7.28 (9 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 3a-H caused enhancement of 4-H (6) and 11b-H (7); *m/z* (%) 360 (M^+, 14), 255 (100), and 104 (15).

2,3,3aα,4β,6,11,11aα,11bα- *and* 2,3,3aα,4α,6,11,11aβ,11bα-*Octahydro-4-(4-dimethylaminophenyl)-2-methyl-1H-pyrrolo*-[3′,4′:3,4]*pyrrolo*[1,2-b]*isoquinoline-1,3-dione* (**10c**) *and* (**11c**).—Prepared from tetrahydroisoquinoline-1-carboxylic acid, *p*-dimethylaminobenzaldehyde, and *N*-methylmaleimide by the general method. Heating at 120 °C in DMF was continued for 10 h at which time unchanged aldehyde was still present. The crude isomer mixture was separated by flash chromatography eluting with 3:1 v/v toluene–ether. The first fraction contained unchanged aldehyde and was followed by (**10c**) (27%) and (**11c**) (26%). Based on the amount of aldehyde consumed this represents a combined yield of 66%.

Compound (**10c**). Pale cream rods (ethanol), m.p. 180—182 °C (Found: C, 73.35; H, 6.75; N, 11.1. $C_{23}H_{25}N_3O_2$ requires C, 73.6; H, 6.7; N, 11.2%); $\nu_{max.}$ 1 760, 1 680 (amide), 795, and 737 cm^{-1}; δ 2.68 (1 H, m, 11-H), 2.96 (6 H, s, NMe_2), 3.03 (3 H, s, 2-Me), 3.09 (1 H, dd, *J* 4 and 16 Hz, 11-H), 3.26 (1 H, d, *J* 15 Hz, 6-H), 3.40 (1 H, m, 11a-H), 3.48 (1 H, d, *J* 8 Hz, 3a-H), 3.71 (1 H, t, *J* 8 Hz, 11b-H), 3.77 (1 H, d, *J* 15 Hz, 6-H), 4.73 (1 H, s, 4-H), 6.72 (2 H, d, *J* 9 Hz, ArH), 6.89—7.08 (4 H, m, ArH), and 7.08 (2 H, d, *J* 9 Hz, ArH); *m/z* (%) 375 (M^+, 100) and 264(59). Stereochemistry was assigned by comparison of the ^{1}H n.m.r. spectrum with that of (**10**; R = Ph).[1]

Compound (**11c**). Tan platelets (ethanol), m.p. 207—209 °C (Found: C, 73.4; H, 6.7; N, 11.1); $\nu_{max.}$ 1 760, 1 685 (amide), 760, 750, and 710 cm^{-1}; δ 2.87 (2 H, d, *J* 8 Hz, 11-H), 2.94 (3 H, s, 2-Me), 2.96 (6 H, s, NMe_2), 3.16 (1 H, d, *J* 8 Hz, 11b-H), 3.49 (1 H, t, *J* 8 Hz, 3a-H), 3.64 (1 H, d, *J* 17 Hz, 6-H), 4.07 (1 H, d, *J* 17 Hz, 6-H), 4.11 (1 H, t, *J* 8 Hz, 11a-H), 4.30 (1 H, d, *J* 8 Hz, 4-H), 6.73 (2 H, d, *J* 8 Hz, ArH), 6.87—7.16 (4 H, m, ArH), and 7.07 (2 H, d, *J* 8 Hz, ArH); *m/z* (%) 375 (M^+, 100) and 264 (41). Stereochemistry was assigned by comparison of the ^{1}H n.m.r. spectrum with that of (**11**; R = Ph).[1]

2,3,3aα,4β,6,11,11aα,11bα-, 2,3,3aα,4α,6,11,11aβ,11bα-, *and* 2,3,3aα,4β,6,11,11aβ,11bα-*Octahydro-2-methyl-4-(4-nitrophenyl)-1H-pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-b]*isoquinoline-1,3-dione* (**10d**), (**11d**), *and* (**13b**).—Prepared from tetrahydroisoquinoline-1-carboxylic acid, *p*-nitrobenzaldehyde, and *N*-methylmaleimide by the general procedure (DMF, 120 °C, 0.5 h). The crude isomer mixture was separated by flash chromatography eluting with 3:1 v/v toluene–ether to give first (**13b**) (6%), followed by (**10d**) (50%), and finally (**11d**) (40%).

Compound (**10d**). Pale yellow prisms (ether–hexane), m.p. 110—113 °C (decomp.) (Found: C, 66.95; H, 5.1; N, 11.1. $C_{21}H_{19}N_3O_4$ requires C, 66.8; H, 5.1; N, 11.1%); $\nu_{max.}$ 1 765, 1 690 (amide), 1 340 (nitro), 755, 750, 735, and 700 cm^{-1}; δ 2.66 (1 H, dd, *J* 11 and 16 Hz, 11-H), 3.06 (3 H, s, 2-Me), 3.09 (1 H, dd, *J* 4 and 16 Hz, 11-H), 3.34 (1 H, d, *J* 15 Hz, 6-H), 3.47 (1 H, dd, *J* 1.5 and 8 Hz, 3a-H), 3.55 (1 H, m, 1a-H), 3.79 (1 H, t, *J* 8 Hz, 11b-H), 3.80 (1 H, d, *J* 15 Hz, 6-H), 4.81 (1 H, d, *J* 1.5 Hz, 4-H), 6.89—7.11 (4 H, m, ArH), 7.45 (2 H, d, *J* 9 Hz, ArH), and 8.28 (2 H, d, *J* 9 Hz, ArH); *m/z* (%) 377 (M^+, 40), 266 (20), and 104 (100). Stereochemistry was assigned by comparison of the ^{1}H n.m.r. spectrum with that of (**10**; R = Ph).[1]

Compound (**11d**). Pale yellow prisms (methanol), m.p. 257—259 °C (Found: C, 66.7; H, 5.1; N, 10.9); $\nu_{max.}$ 1 760, 1 690 (amide), 1 340 (nitro), 758, and 695 cm^{-1}; δ 2.89 (2 H, d, *J* 7 Hz, 11-H), 2.93 (3 H, s, 2-Me), 3.22 (1 H, d, *J* 8 Hz, 11b-H), 3.53 (1 H, d, *J* 16 Hz, 6-H), 3.56 (1 H, t, *J* 8.5 Hz, 3a-H), 4.19 (1 H, t, *J* 7 Hz, 11a-H), 4.21 (1 H, d, *J* 16 Hz, 6-H), 4.45 (1 H, d, *J* 9 Hz, 4-H), 6.87—7.20 (4 H, m, ArH), 7.44 (2 H, d, *J* 9 Hz, ArH), and 8.22 (2 H, d, *J* 9 Hz, ArH); *m/z* (%) 377 (M^+, 43), 266 (13), and 104 (100). Stereochemistry was assigned by comparison of the ^{1}H n.m.r. spectrum with that of (**11**; R = Ph).[1]

Compound (**13b**). Pale yellow prisms (benzene–hexane), m.p. 168—171 °C (Found: C, 66.5; H, 4.95; N, 11.2); $\nu_{max.}$ 1 765, 1 690 (amide), 1 340 (nitro), 750, and 700 cm^{-1}; δ([$^2H_5$]pyridine), 2.90 (1 H, m, 11a-H), 2.99 (3 H, s, 2-Me), 3.16 (1 H, dd, *J* 11 and 15 Hz, 11-H), 3.13 (1 H, d, *J* 14 Hz, 6-H), 3.17 (1 H, dd, *J* 4 and 15 Hz, 11-H), 3.52 (2 H, m, 3a- and 11b-H), 3.82 (1 H, d, *J* 7 Hz, 4-H), 3.86 (1 H, d, *J* 14 Hz, 6-H), 7.07—7.22 (4 H, m, ArH), 7.79 (2 H, d, *J* 9 Hz, ArH), and 7.99 (2 H, d, *J* 9 Hz, ArH); ^{1}H

NOEDSY (%); irradiation of 4-H caused enhancement of 3a-H (1.3) and 11a-H (4); irradiation of 11a-H caused enhancement of 4-H (4) and 11b-H (1); *m/z* (%) 377 (M^+, 67), 266 (15), 104 (84), and 28 (100).

1,2,3,3a,4,8,8a,8b-*Octahydro*-2-*methyl*-4-(2-*phenylethenyl*)-*pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-c]*thiazole*-1,3-*dione* (**15a**)—(**18a**).—A mixture of thiazolidine-4-carboxylic acid (3.0 g, 0.023 mol), *trans*-cinnamaldehyde (2.97 g, 0.023 mol), and *N*-methylmaleimide (2.5 g, 0.023 mol) in dry acetonitrile (50 ml) was stirred and boiled under reflux under a nitrogen atmosphere for 18 h. Unchanged thiazolidinecarboxylic acid (280 mg) was filtered off from the cooled reaction mixture and the filtrate was evaporated under reduced pressure. The residue was dissolved in chloroform, washed with water, dried ($MgSO_4$), and evaporated to give an orange gum the ^{1}H n.m.r spectrum of which showed it to consist of a 2.03:1.11:1.96:1.0 mixture of (**15a**)—(**18a**). The mixture was separated by flash chromatography eluting with 7:3 v/v ether–light petroleum to afford a combined yield of (**15a**)—(**18a**) and mixed isomer fractions of 91%.

Compound (**15a**). Colourless rods (1.16 g, 20%) from methanol–chloroform, m.p. 166—167 °C; δ 2.44 (1 H, dd, *J* 9.9 and 10.7 Hz, 8β-H), 2.98 (3 H, s, NMe), 3.09 (1 H, dd, *J* 7.3 and 10.9 Hz, 8α-H), 3.34 (1 H, t, 3a-H), 3.44 (1 H, t, 4α-H), 3.83 (1 H, dd, *J* 8.3 and 9.2 Hz, 8b-H), 3.95 (1 H, m, 8a-H), 4.16 (2 H, AB, 6-H_2), 6.16 (1 H, dd, PhCH=C*H*), 6.67 (1 H, d, *J* 15.8 Hz, PhCH), and 7.24—7.43 (5 H, m, ArH).

Compound (**16a**). Colourless prisms (1.02 g, 17.5%) from chloroform–ether, m.p. 204—206 °C (Found: C, 64.90; H, 5.85; N, 9.15. $C_{17}H_{18}N_2O_2S$ requires C, 64.95; H, 5.75; N, 8.9%); δ 2.71 (1 H, t, 8β-H), 3.05 (3 H, s, NMe), 3.27 (1 H, dd, *J* 10.1 and 10.3 Hz, 8α-H), 3.32 (1 H, d, *J* 7.4 Hz, 8b-H), 3.46 (1 H, t, 3a-H), 3.63 (1 H, t, 4α-H), 3.88 (1 H, dd, *J* 7.7 and 9.6 Hz, 8a-H), 4.16 (2 H, s, 6-H_2), 6.09 (1 H, dd, PhCH=C*H*), 6.65 (1 H, d, *J* 15.7 Hz, PhCH), and 7.27—7.45 (5 H, m, ArH); *m/z* (%) 314 (M^+, 100), 313 (11), 281 (13), 268 (74), 267 (99), 223 (47), 210 (13), 182 (19), 156 (24), 128 (10), 117 (19), 115 (24), and 91 (18).

Compound (**17a**). Colourless needles (710 mg, 12%) from chloroform, m.p. 187—188 °C; δ 3.00 (2 H, m, 8α-H and 8aβ-H), 3.02 (3 H, s, NMe), 3.21 (2 H, m, 8β-H and 8b-H), 3.26 (1 H, d, *J* 6.3 Hz, 6β-H), 3.35 (1 H, t, 4β-H), 3.62 (1 H, t, 3a-H), 3.78 (1 H, d, 6α-H), 6.13 (1 H, dd, *J* 9.1 and 15.7 Hz, PhCH=C*H*), 6.64 (1 H, d, PhCH), and 7.20—7.45 (5 H, m, ArH).

Compound (**18a**). Colourless prisms (320 mg, 5.5%) from chloroform, m.p. 189—190 °C; δ 2.51 (1 H, t, 8β-H), 3.05 (3 H, s, NMe), 3.32 (1 H, d, *J* 8.2 Hz, 8b-H), 3.42 (1 H, t, 8α-H), 3.43 (1 H, d, *J* 8.6 Hz, 3a-H), 3.83 (1 H, dd, *J* 7.7 and 10.0 Hz, 8aβ-H), 4.13 (2 H, AB, *J* 9.6 Hz, 6-H_2), 4.19 (1 H, d, *J* 11.9 Hz, 4β-H), 6.02 (1 H, dd, PhCH=C*H*), 6.67 (1 H, d, *J* 15.3 Hz, PhCH), and 7.27—7.43 (5 H, m, ArH). In addition isomeric mixtures (2.61 g, 45%) were obtained from the flash chromatography.

1,2,3,3aα,4β,8,8aα,8bα- *and* 1,2,3,3aα,4α,8,8aβ,8bα-*Octahydro*-2-*methyl*-4-(2-*phenylethyl*)*pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-c]*thiazole*-1,3-*dione* (**15b**) *and* (**16b**).—A mixture of thiazolidine-4-carboxylic acid (1.0 g, 7.52 mmol), 3-phenylpropionaldehyde (1.0 g, 7.46 mmol), and *N*-methylmaleimide (840 mg, 7.56 mmol) in acetonitrile (25 ml) was stirred and boiled under reflux for 16 h. The solution was then cooled and filtered to remove unchanged thiazolidine-4-carboxylic acid (145 mg) and the filtrate evaporated to dryness to leave an orange gum (2.27 g) the ^{1}H n.m.r. spectrum of which showed it to consist of a 1.5:1 mixture of (**15b**) and (**16b**) which was separated by flash chromatography eluting with 9:1 chloroform–light petroleum.

Compound (**15b**). Obtained as a colourless semi-solid (990 mg, 44%); δ 2.45 (1 H, dd, *J* 9.3 and 10.8 Hz, 8-H), 1.92, 2.14, 2.90, and 3.01 (4 × m, 4 × 1 H, $PhCH_2CH_2$), 3.03 (1 H, m, 8-H), 3.04 (3 H, s, Me), 3.09 (1 H, m, 4-H), 3.29 (1 H, dd, *J* 7.4 and 9.3 Hz, 3a-H), 3.83 (1 H, t, *J* 8.7 Hz, 8b-H), 3.95 (1 H, dd, *J* 9.0 and 9.2 Hz, 8a-H), 4.17 and 4.28 (2 × 1 H, 2 × d, *J* 10.2 Hz, 6-H), and 7.31 (5 H, m, ArH).

Compound (**16b**). Colourless prisms (660 mg, 29%) from methanol, m.p. 116 °C (Found: C, 64.60; H, 6.50; N, 8.95. $C_{17}H_{20}N_2O_2S$ requires C, 64.55; H, 6.35; N, 8.85%); δ 1.90, 2.65, 3.12 (2 H + 2 × 1 H, m, $PhCH_2CH_2$), 2.68 (1 H, t, *J* 10.0 Hz, 8β-H), 3.08 (3 H, s, Me), 3.19 (1 H, m, 4-H), 3.27 (1 H, dd, *J* 7.6 and 10.4 Hz, 8α-H), 3.33 (1 H, d, *J* 7.9 Hz, 8b-H), 3.53 (1 H, t, *J* 7.9 Hz, 3a-H), 3.86 (1 H, dd, *J* 7.6 and 9.7 Hz, 8a-H), 4.26 (2 H, s, NCH_2S), and 7.31 (5 H, m, ArH); *m/z* (%) 316 (M^+, 60), 269 (25), 211 (100), 166 (35), 117 (13), 91 (45), 83 (70), and 80 (14).

Cycloadditions of Tetrahydroisoquinoline-1-*carboxylic Acid.*—(*a*) *At ambient temperature in DMF.* A mixture of tetrahydroisoquinoline-1-carboxylic acid (886 mg, 5 mmol), benzaldehyde (531 mg, 5 mmol), and *N*-methylmaleimide (556 mg, 5 mmol) in DMF (30 ml) was stirred at ambient temperature (*ca.* 21 °C) for 120 h. Unchanged tetrahydroisoquinoline-1-carboxylic acid was removed by filtration and the filtrate evaporated to dryness under reduced pressure to afford a gum. The gum was dissolved in chloroform, washed with water, dried (Na_2SO_4), and the solvent evaporated. The crude product was then analysed by 250 MHz n.m.r. spectroscopy and found to consist of a 2.7:4.8:1:1.8 mixture of (**21a**)—(**24a**) by comparison with the ^{1}H n.m.r. spectra of authentic samples.[1]

(*b*) *In toluene at* 110 °C. A similar reaction was carried out in boiling toluene (50 ml) for 44 h at which time all solids had dissolved. Work-up as before gave a crude product the 250 MHz ^{1}H n.m.r. spectrum of which showed it to consist of a 1.7:3.2:1.0:3.1 mixture of (**21a**)—(**24a**).

2,3,3a,4,6,7,11b,11c-*Octahydro*-2-*methyl*-4-(2-*pyridyl*)-1H-*pyrrolo*[3′,4′:3,4]*pyrrolo*[2,1-a]*isoquinoline*-1,3-*dione* (**21b**)—(**24b**).—(*a*) *In DMF.* The reaction was carried out by the general method and the crude product was shown to comprise a 2.5:1.0:1.3:2.5 mixture of (**21b**)—(**24b**) which were separated by flash chromatography eluting with 5:2 v/v benzene–ether, followed by ethyl acetate, and finally ethanol for the final component to give (**22b**) (13%), (**24b**) (31%), (**21b**) (35%), and (**23b**) (20%).

2,3,3aα,4β,6,7,11bα,11c-*Octahydro isomer* (**21b**). Colourless needles (ethanol), m.p. 207—209 °C (Found: C, 71.8; H, 6.0; N, 12.8. $C_{20}H_{19}N_3O_2$ requires C, 72.05; H, 5.7; N, 12.6%); $\nu_{max.}$ 1 760, 1 690 (amide), 780, 755, and 750 cm^{-1}; δ 2.46 (1 H, m, 7-H), 2.97 (3 H, s, Me), 3.07 (3 H, m, 6- and 7-H), 3.55 (2 H, m, 3a- and 11c-H), 4.57 (1 H, d, *J* 7 Hz, 11b-H), 5.02 (1 H, s, 8-H), 7.07—7.73 (7 H, m, ArH), and 8.59 (1 H, m, α-pyridine-H); ^{1}H NOEDSY (%) (C_6D_6):irradiation of 4-H caused enhancement of 3a-H (4) and the α-pyridine-H (5); irradiation of 11b-H caused enhancement of 11c-H (16) and ArH (4); *m/z* (%) 333 (M^+, 100) and 222 (35).

2,3,3aα,4α,6,7,11bβ,11cα-*Octahydro isomer* (**22b**). Colourless prisms (ethanol), m.p. 165—168 °C (Found: C, 72.3; H, 5.9; N, 12.4); $\nu_{max.}$ 1 770, 1 690 (amide), and 755 cm^{-1}; δ 2.42 (1 H, m, 7-H), 2.87 (3 H, m, 6- and 7-H), 2.89 (3 H, s, Me), 3.87 (1 H, t, *J* 8 Hz, 3a-H), 4.06 (1 H, d, *J* 8 Hz, 11c-H), 4.63 (1 H, d, *J* 8 Hz, 4-H), 4.76 (1 H, s, 11b-H), 7.03—7.72 (7 H, m, ArH), and 8.58 (1 H, m, α-pyridine-H); ^{1}H NOEDSY (%) (C_6D_6):irradiation of 3a-H caused enhancement of 4-H (13), γ-pyridyl-H (7), and 11c-H (11); irradiation of 4-H caused enhancement of 3a-H (15), α-pyridyl-H (1), and γ-pyridyl-H (4); irradiation of 11b-H caused enhancement of 11c-H (7) and ArH (11); irradiation of 11c-H caused enhancement of 3a-H (11) and 11b-H (5); *m/z* (%) 333 (M^+, 100) and 241 (86).

2,3,3aα,4α,6,7,11bα,11cα-*Octahydro isomer* (**23b**). Colourless rods (ethanol), m.p. 196—198 °C (Found: C, 72.3; H, 6.0; N,

12.55); $\nu_{max.}$ 1 760, 1 690 (amide), and 750 cm^{-1}; δ 2.37 (1 H, m, 7-H), 2.75 (1 H, m, 6-H), 2.79 (3 H, s, Me), 3.09 (2 H, m, 6- and 7-H), 3.69 (1 H, dd, *J* 7 and 9 Hz, 3a-H), 3.79 (1 H, t, *J* 7 Hz, 11c-H), 3.97 (1 H, d, *J* 7 Hz, 11b-H), 4.02 (1 H, d, *J* 9 Hz, 4-H), 7.13—7.69 (7 H, m, ArH), and 8.65 (1 H, m, α-pyridine-H); *m/z* (%) 333 (M^+, 15) and 130 (100). Stereochemistry was assigned by comparison of the ^1H n.m.r. spectra with the 4-phenyl analogues.[1]

2,3,3aα,4β,6,7,11bβ,11cα-*Octahydro isomer* (**24b**). Colourless prisms (ethanol–hexane), m.p. 147—150 °C (Found: C, 71.95; H, 5.9; N, 12.4); $\nu_{max.}$ 1 760, 1 690 (amide), and 760 cm^{-1}; δ 2.51 (1 H, m, 7-H), 2.92 (3 H, m, 6- and 7-H), 3.07 (3 H, s, 2-Me), 3.63 (3 H, m, 3a-, 4-, and 11b-H), 3.80 (1 H, t, *J* 8 Hz, 11c-H), 7.08—7.97 (7 H, m, ArH), and 8.71 (1 H, m, α-pyridine-H); *m/z* (%) 333 (M^+, 24) and 130 (100). Stereochemistry was assigned by comparison of the ^1H n.m.r. spectra with the 4-phenyl analogues.[1]

(*b*) *In acetonitrile.* The reaction was carried out at 80 °C for 2.33 h in acetonitrile. The crude product was shown by 400 MHz ^1H n.m.r. to consist of a 2.0:1.0:1.3:1.9 mixture of (**21b**)—(**24b**). The spectra of the adducts were identical to those reported above.

(*c*) *By cycloreversion of oxazolidine* (**28**). A mixture of 2α,3β,6,10bα-tetrahydro-2,3-di(2-pyridyl)-5*H*-oxazolo[2,3-*a*]-isoquinoline (1 mmol) and *N*-methylmaleimide (1 mmol) was boiled under reflux in acetonitrile (25 ml) for 6 h when n.m.r. monitoring showed the reaction to be complete. Comparison of the ^1H n.m.r. spectra and t.l.c. behaviour with authentic samples showed the reaction mixture consisted of a 2.1:1 mixture of (**21b**) and (**22b**) together with pyridine-2-carbaldehyde.

3,6-*Dimethyl*-2,4-*dioxo*-8-*phenyl*-3,7-*diazabicyclo*[3.3.0]-*octane* (**30a**)—(**33a**).—*At* 153 °C. Prepared (100%) by the general procedure with a reaction time of 35 min. The ^1H n.m.r. spectrum of the product showed it to consist of a mixture of (**30a**)—(**33a**) (Table).

Compound (**30a**). Colourless needles from ethanol, m.p. 113—115 °C (Found: C, 68.65; H, 6.55; N, 11.40. $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.60; N, 11.45%); $\nu_{max.}$ 3 440, 1 770, 1 690, and 1 440 cm^{-1}; δ 1.34 (3 H, d, Me), 2.87 (3 H, s, NMe), 3.00 (1 H, d, *J* 7.6 Hz, 1-H), 3.42 (1 H, t, 5-H), 4.08 (1 H, q, 8-H), 4.81 (1 H, d, *J* 8.6 Hz, 6-H), and 7.31 (5 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (**12**); irradiation of 5-H caused enhancement of 6-H (7.5) and 1-H (7.5); irradiation of 1-H caused enhancement of 5-H (9.5) and 8-H (3.5); irradiation of 8-H caused enhancement of 1-H (4); *m/z* (%) 244 (M^+, 41), 243 (13), 229 (10), 158 (6), 144 (11), 133 (100), 132 (65), and 91 (8).

Compound (**31a**). Colourless plates from ethanol, m.p. 75—80 °C; δ 1.29 (3 H, d, Me), 3.03 (3 H, s, NMe), 3.23 (1 H, t, 1-H), 3.52 (1 H, dd, *J* 1.4 and 7.8 Hz, 5-H), 3.64 (1 H, m, 8-H), 4.81 (1 H, s, 6-H), and 7.36 (5 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (5); irradiation of 5-H caused enhancement of 6-H (3.5) and 1-H (5.5); irradiation of 1-H caused enhancement of 5-H (8.5) and 8-H (8.5).

Compound (**32a**). Colourless needles from ethanol, m.p. 135—140 °C; δ 1.42 (3 H, s, Me), 2.87 (3 H, s, NMe), 3.08 (1 H, t, 1-H), 3.32 (1 H, t, 5-H), 3.48 (1 H, m, 8-H), 4.40 (1 H, d, *J* 8.0 Hz, 6-H), and 7.32 (5 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (6) and 8-H (4); irradiation of 5-H caused enhancement of 6-H (4.5) and 1-H (4.5); irradiation of 1-H caused enhancement of 5-H (4.5) and 8-H (4).

Compound (**33a**). Colourless solid, δ 1.50 (3 H, d, Me), 3.01 (4 H, d + m, NMe + H), 3.31 (2 H, m), 4.28 (1 H, d, 6-H), and 7.37 (5 H, m, ArH).

The reaction was repeated at 120 °C for 55 min and at 40 °C for 7 days giving different ratios of (**30a**)—(**33a**) (Table).

6-*Benzyl*-3-*methyl*-2,4-*dioxo*-8-*phenyl*-3,7-*diazabicyclo-octane* (**30b**)—(**33b**).—The reaction was carried out by the general procedure at 153 °C for 30 min and gave a product (98%), the ^1H n.m.r. spectrum of which showed it to consist of a 4:1.3:1:1.1 mixture of (**30b**)—(**33b**). The reaction was repeated at 100 °C for 75 min and at 60 °C for 18.5 h giving different ratios of (**30b**)—(**33b**) (Table).

Compound (**30b**). Colourless needles from ethanol, m.p. 121—123 °C (Found: C, 74.70; H, 6.25; N, 8.80. $C_{20}H_{20}N_2O_2$ requires C, 74.95; H, 6.30; N, 8.75%); $\nu_{max.}$ 3 420, 1 770, and 1 690 cm^{-1}; δ 2.86 (3 H, s, NMe), 2.94 (2 H, m, $PhCH_2$), 3.14 (1 H, d, *J* 7.6 Hz, 1-H), 3.47 (1 H, t, 5-H), 4.13 (1 H, dd, *J* 5.9 and 9.7 Hz, 8-H), 4.82 (1 H, d, *J* 8.7 Hz, 6-H), and 7.3 (10 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (14.5); irradiation of 5-H caused enhancement of 6-H (8.5) and 1-H (11.5); irradiation of 1-H caused enhancement of 5-H (15) and 8-H (4); irradiation of 8-H caused enhancement of 1-H (3); *m/z* (%) 320 (M^+, 0.25), 230 (15), 229 (100), 209 (2), 144 (19), 104 (6), and 91 (9).

Compound (**31b**). Colourless plates from ethanol, m.p. 133—135 °C; δ 2.53 (1 H, dd, *J* 10.2 and 13.8 Hz, PhC*H*H), 3.09 (3 H, s, Me), 3.31 (1 H, dd, *J* 3.7 and 13.6 Hz, PhC*H*H), 3.36 (1 H, t, *J* 7.9 Hz, 1-H), 3.48 (1 H, dd, *J* 1.6 and 7.9 Hz, 5-H), 3.80 (1 H, m, 8-H), 4.76 (1 H, s, 6-H), and 7.3 (10 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (4); irradiation of 8-H caused enhancement of 1-H (15.5).

Compound (**32b**). Colourless needles from ethanol, m.p. 175—177 °C; δ 2.83 (1 H, dd, PhC*H*H), 2.94 (3 H, s, NMe), 3.22 (1 H, t, 1-H), 3.35 (1 H, t, 5-H), 3.40 (1 H, dd, PhC*H*H), 3.51 (1 H, m, 8-H), 4.29 (1 H, d, *J* 8.2 Hz, 6-H), and 7.30 (10 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (7.5) and 8-H (5.5); irradiation of 5-H caused enhancement of 6-H (5); irradiation of 1-H caused enhancement of 5-H (4.5) and 8-H (5); irradiation of 8-H caused enhancement of 6-H (5) and 1-H (5.5).

Compound (**33b**). Colourless needles from ethanol, m.p. 109—111 °C; δ 2.90 (1 H, dd, PhC*H*H), 3.01 (3 H, s, NMe), 3.10 (1 H, dd, *J* 7.8 and 9.4 Hz, 1-H), 3.20 (1 H, dd, *J* 7.2 and 9.4 Hz, 5-H), 3.34 (1 H, dd, PhC*H*H), 3.43 (1 H, m, 8-H), 4.14 (1 H, d, *J* 7.2 Hz, 6-H), and 7.34 (10 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 8-H (4); irradiation of 8-H caused enhancement of 6-H (4).

3-*Methyl*-6-(2-*methylthioethyl*)-2,4-*dioxo*-8-*phenyl*-3,7-*diaza-bicyclo*[3.3.0]*octane* (**30c**)—(**33c**).—The reaction was carried out by the general procedure at 153 °C for 40 min and gave a product (98%) the ^1H n.m.r. spectrum of which showed it to consist of a mixture of (**30c**)—(**33c**) (Table). The reaction was repeated at 100 °C for 90 min and at 60 °C for 22 h giving different ratios of (**30c**)—(**33c**) (Table).

Compound (**30c**). Yellow oil, δ 1.90 (2 H, m, CH_2) 2.15 (3 H, s, SMe), 2.61 (2 H, t, CH_2), 2.87 (3 H, s, NMe), 3.06 (1 H, d, 1-H), 3.42 (1 H, t, 5-H), 3.97 (1 H, t, 8-H), 4.70 (1 H, d, *J* 8.6 Hz, 6-H), and 7.30 (5-H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (13.5); irradiation of 5-H caused enhancement of 6-H (8) and 1-H (11); irradiation of 1-H caused enhancement of 5-H (14) and 8-H (5); irradiation of 8-H caused enhancement of 1-H (4).

Compound (**31c**). Pale yellow plates from ethanol, m.p. 126—127 °C; δ 1.72 (1 H, m, C*H*H), 2.11 (4 H, s + m, SMe and C*H*H), 3.03 (3 H, s, NMe), 3.27 (1 H, t, 1-H), 3.51 (1 H, dd, *J* 1.4 and 7.8 Hz, 5-H), 3.64 (1 H, m, 8-H), 4.80 (1 H, s, 6-H), and 7.37 (5 H, m, ArH); ^1H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (4.5); irradiation of 5-H caused enhancement of 6-H (4.5) and 1-H (10); irradiation of 1-H caused enhancement of 5-H (8.5) and 8-H (12); irradiation of 8-H caused enhancement of 1-H (14.5).

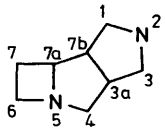
Compound (**32c**). Colourless prisms from ethanol, m.p. 126—

128 °C (Found: C, 63.05; H, 6.45; N, 9.00. $C_{16}H_{20}N_2O_2S$ requires C, 63.15; H, 6.60; N, 9.20%); $\nu_{max.}$ 3 430, 1 760, 1 690, 1 430, and 1 380 cm^{-1}; δ 1.93 (1 H, m, C*H*H), 2.14 (3 H, s, SMe), 2.32 (1 H, m, C*H*H), 2.72 (2 H, m, CH_2), 2.87 (3 H, s, NMe), 3.17 (1 H, t, 1-H), 3.33 (1 H, t, 5-H), 3.47 (1 H, m, 8-H), 4.41 (1 H, d, *J* 8.3 Hz, 6-H), and 7.31 (5 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 6-H caused enhancement of 5-H (6) and 8-H (5); irradiation of 5-H caused enhancement of 6-H (5); irradiation of 1-H caused enhancement of 8-H (5); irradiation of 8-H caused enhancement of 6-H (5) and 1-H (4); *m/z* (%) 304 (M^+, 83), 257 (35), 243 (3), 229 (83), 193 (10), 132 (100), and 61 (21).

Compound (**33c**). Colourless plates from ethanol, m.p. 126—128 °C; δ 1.97 (1 H, m, C*H*H), 2.12 (3 H, 1 s, SMe), 2.19 (1 H, m, C*H*H), 2.71 (2 H, t, CH_2), 2.99 (3 H, s, NMe), 3.03 (1 H, dd, *J* 7.6 and 9.4 Hz, 1-H), 3.24 (1 H, dd, *J* 7.3 and 9.4 Hz, 5-H), 3.36 (1 H, m, 8-H), 4.23 (1 H, d, *J* 7.3 Hz, 6-H), 7.29 (1 H, m, ArH), 7.36 (2 H, m, ArH), and 7.52 (2 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 6-H caused enhancement of 8-H (4); irradiation of 8-H caused enhancement of 6-H (4) and 1-H (2).

1,2,3,3aα,4β,6,7,8,8aα,8bα- *and* 1,2,3,3aα,4α,6,7,8,8aβ,8bα-*Decahydro-2-phenyl-4-t-butylpyrrolo*[3,4-a]*pyrrolizine*-1,3-*dione* (**43**) *and* (**44**).—Compound (**43**). Colourless prisms (ether–hexane), m.p. 89—91 °C (Found: C, 73.1; H, 7.9; N, 8.9. $C_{19}H_{24}N_2O_2$ requires C, 73.0; H, 7.7; N, 9.0%); $\nu_{max.}$ 1 765, 1 700 (amide), 760, 720, and 690 cm^{-1}; δ 0.96 (9 H, s, Bu^t), 1.77 (2 H, m, 7-H), 1.98 (2 H, m, 8-H), 2.61 (1 H, m, 6β-H), 3.18 (2 H, m, 4- and 6α-H), 3.35 (1 H, dd, *J* 3 and 9 Hz, 3a-H), 3.43 (1 H, t, *J* 9 Hz, 11b-H), 3.96 (1 H, m, 8a-H), and 7.22—7.51 (5 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 8a-H caused enhancement of 8b-H (7); irradiation of 8b-H caused enhancement of 8a-H (6); *m/z* (%) 312 (M^+, 1.5) and 255 (100).

Compound (**44**). Colourless rods (ether–benzene), m.p. 108—111 °C (Found: C, 72.8; H, 7.8; N, 8.9); $\nu_{max.}$ 1 770, 1 705 (amide), 750, and 700 cm^{-1}; δ 1.08 (9 H, s, Bu^t), 1.84 (3 H, m, 7-CH_2 and 8-H), 2.18 (1 H, m, 8-H), 2.69 (1 H, m, 6-H), 3.09 (1 H, d, *J* 9 Hz, 4-H), 3.13 (1 H, m, 6-H), 3.19 (1 H, dd, *J* 6 and 9 Hz, 8b-H), 3.75 (1 H, t, *J* 9 Hz, 3a-H), 3.77 (1 H, dd, *J* 6 and 12 Hz, 8a-H), and 7.24—7.52 (5 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 4-H caused enhancement of 3a-H (7); irradiation of 8b-H caused enhancement of 3a-H (8); *m/z* (%) 312, (M^+, 1) and 255 (100).



2,3,3aα,4β,6,7,7aα,7bα-*Octahydro-2-methyl-4-phenyl*-1H-*pyrrolo*[3′,4′:3,4]*pyrrolo*[1,2-a]*azetidine*-1,3-*dione* (**49**).*—Prepared by the general method. Heating was continued for 3 h when t.l.c. monitoring showed the presence of a single new spot. The crude product was purified by flash chromatography eluting with 2:1 v/v ether–light petroleum followed by crystallization from ether–hexane to afford the *product* as colourless prisms, m.p. 69—72 °C; *m/z* 256.12158. $C_{15}H_{16}N_2O_2$ requires 256.12117; $\nu_{max.}$ 1 760, 1 690, and 710 cm^{-1}; δ 1.92 (1 H, m, 7β-H), 2.67 (1 H, m, 7α-H), 3.02 (1 H, dd, *J* 9 and 18 Hz, 6β-H), 3.05 (3 H, s, NMe), 3.55 (1 H, dd, *J* 1.4 and 9 Hz, 3a-H), 3.61 (1 H, t, *J* 9 Hz, 7b-H), 3.67 (1 H, m, 6α-H), 4.52 (1 H, m, 7a-H), 4.57 (1 H, br s, 4-H), and 7.19—8.03 (5 H, m, ArH); ^{1}H NOEDSY (%): irradiation of 3a-H caused enhancement of 4-H (2); irradiation of 6α-H caused enhancement of 6β-H (18), 7α-H (3), and ArH (0.5); irradiation of 7α-H caused enhancement of 6α-H (3), 7β-H (17), and 7a-H (3); irradiation of 7b-H caused enhancement of 7a-H (6) and ArH (2.3); *m/z* (%) 256 (M^+, 32), 165 (100), and 145 (15).

Note added in proof. Such effects were subsequently observed in intramolecular cycloadditions to non-activated alkenes.[27]

* 2,3,3a,4,6,7,7a,7b-Octahydro-1*H*-pyrrolo[3′,4′:3,4]pyrrolo[1,2-*a*]-azetidine skeleton.

Acknowledgements

We thank Glaxo Laboratories (Ware), Gallahers Ltd., D.E.N.I., S.E.R.C., and Queen's University for support.

References

1 Part 11, R. Grigg, S. Surendrakumar, S. Thianpatanagul, and D. Vipond, *J. Chem. Soc., Perkin Trans. 1*, 1988, preceding paper.
2 Preliminary communication: R. Grigg, J. Idle, P. McMeekin, and D. Vipond, *J. Chem. Soc., Chem. Commun.*, 1987, 49.
3 R. Grigg and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1984, 180; R. Grigg, M. F. Aly, V. Sridharan, and S. Thianpatanagul, *ibid.*, p. 182.
4 M. F. Aly, R. Grigg, S. Thianpatanagul, and V. Sridharan, *J. Chem. Soc., Perkin Trans. 1*, 1988, 949.
5 R. Hoffmann and R. A. Olofson, *J. Am. Chem. Soc.*, 1966, **88**, 943.
6 M. J. S. Dewar, M. A. Fox, and D. J. Nelson, *J. Organomet. Chem.*, 1980, **185**, 157.
7 H. Yasuda, Y. Ohnuma, M. Yamauchi, H. Tani, and A. Nakamura, *Bull. Chem. Soc. Jpn.*, 1979, **52**, 2036; H. Yasuda, M. Yamauchi, Y. Ohnuma, and A. Nakamura, *ibid.*, 1981, **54**, 1481.
8 R. Grigg, H. Q. N. Gunaratne, V. Sridharan, S. Thianpatanagul, and M. Tute, *Tetrahedron Lett.*, 1983, **24**, 4363.
9 K. Amornraksa, R. Grigg, H. Q. N. Gunaratne, J. Kemp, and V. Sridharan, *J. Chem. Soc., Perkin Trans. 1*, 1987, 2285.
10 H. Ardill, R. Grigg, V. Sridharan, S. Surendrakumar, S. Thianpatanagul, and S. Kanajun, *J. Chem. Soc., Chem. Commun.*, 1986, 602.
11 G. Bianchi, C. De Micheli, and R. Gandolfi, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 721; G. Bianchi and R. Gandolfi in '1,3-Dipolar Cycloaddition Chemistry,' ed. A. Padwa, Wiley Interscience, 1984, vol. 2, p. 451.
12 R. Grigg, J. F. Malone, T. Mongkolaussavaratana, and S. Thianpatanagul, *J. Chem. Soc., Chem. Commun.*, 1986, 421.
13 D. Seebach, M. Boes, R. Naef, and W. B. Schweizer, *J. Am. Chem. Soc.*, 1983, **105**, 5390.
14 A. Eschenmoser, *Chem. Soc. Rev.*, 1976, **5**, 377.
15 K. Burger, A. Meffert, and S. Bauer, *J. Fluorine Chem.*, 1977, **10**, 57.
16 R. Huisgen, H. Gotthardt, H. O. Bayer, and C. F. Schaefer, *Angew. Chem., Int. Ed. Engl.*, 1964, **3**, 136; R. Huisgen, 'Aromaticity,' Chem. Soc. Special Publication No. 21, 1967, p. 51; R. Huisgen, H. Gotthardt, and H. O. Bayer, *Chem. Ber.*, 1970, **103**, 2368; R. Huisgen, H. Gotthardt, and H. O. Bayer, *J. Am. Chem. Soc.*, 1970, **92**, 4340.
17 A. Padwa, R. Lim, J. G. MacDonald, H. L. Gingrich, and S. M. Keller, *J. Org. Chem.*, 1985, **50**, 3816.
18 K. T. Potts, J. Baum, E. Houghton, D. N. Roy, and U. P. Singh, *J. Org. Chem.*, 1974, **39**, 3619.
19 R. N. Pratt, D. P. Stokes, and G. A. Taylor, *J. Chem. Soc., Perkin Trans. 1*, 1975, 498; M. Hafiz and G. A. Taylor, *ibid.*, 1980, 1700; C. P. Falshaw, N. A. Hashi, and G. A. Taylor, *ibid.*, 1985, 1837; M. A. Abou-Gharbia and M. M. Joullie, *J. Org. Chem.*, 1979, **44**, 2961.
20 A. F. Gettins, D. P. Stokes, G. A. Taylor, and C. B. Judge, *J. Chem. Soc., Perkin Trans. 1*, 1977, 1849.
21 R. Huisgen and H. Mäder, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 604.
22 H. Hermann, R. Huisgen, and H. Mäder, *J. Am. Chem. Soc.*, 1971, **93**, 1779.
23 R. Huisgen, W. Scheer, H. Mäder, and E. Brunn, *Angew. Chem., Int. Ed. Engl.*, 1969, **8**, 604.
24 C. Agami and T. Rizk, *Tetrahedron*, 1985, **41**, 537; M. E. A. Astudillo, N. C. J. Chokotho, T. C. Jarvis, C. D. Johnson, C. C. Lewis, and P. D. McDonnell, *ibid.*, 1985, **41**, 5919; S. L. Spassov, L. Markova, O. Argiro, and T. Obretenov, *J. Mol. Struct.*, 1986, **147**, 105.

25 G. Donegan and R. Grigg, unpublished results.
26 R. Grigg, H. Q. N. Gunaratne, and J. Kemp, *J. Chem. Soc., Perkin Trans. 1*, 1984, 41.
27 H. E. Ardill, R. Grigg, V. Sridharan, and S. Surendrakumar, *Tetrahedron*, 1988, **44**, 4953.

Received 17*th July* 1987; *Paper* 7/1288