Tetrahedron Vol. 46, No. 6, pp. 2213-2230, 1990
Printed in Great Britain

0040-4020/90 $3.00+.00

X = Y - ZH Systems as Potential 1,3-Dipoles. Part 27.[1]

Intramolecular Cycloaddition Reactions of Imines of Cyclic Secondary α-Amino Esters. Dipole and Cycloaddition Stereochemistry

Ronald Grigg,*[a] Linda M. Duffy,[b] Michael J. Dorrity,[b] John F. Malone,[b] Shuleewan Rajviroongit[a] and Mark Thornton-Pett.[a]

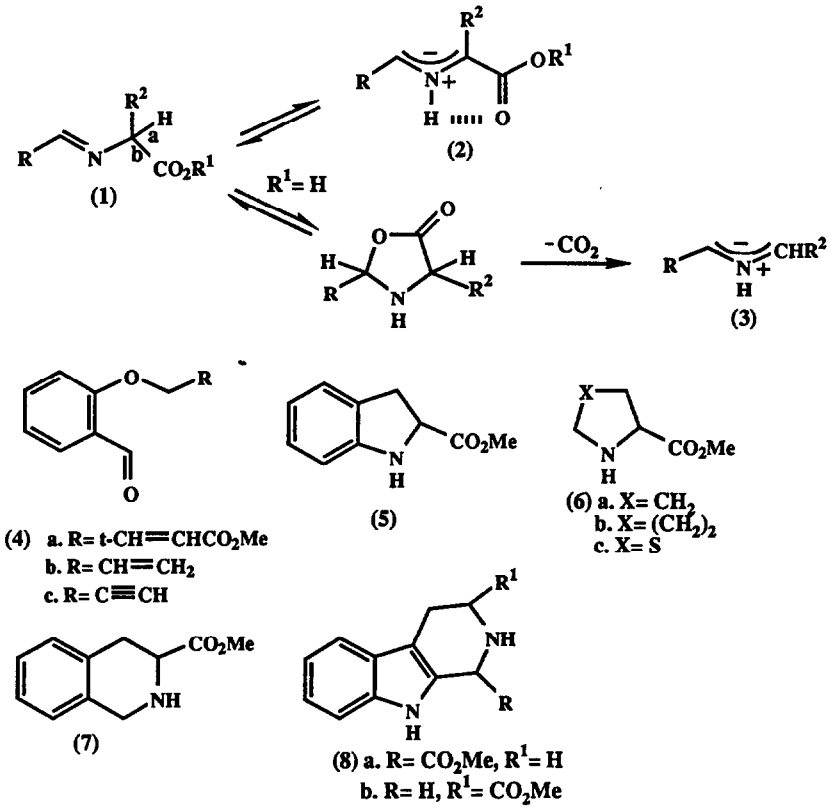
a. School of Chemistry, University of Leeds, Leeds LS2 9JT.
b. Chemistry Department, Queen's University, Belfast, BT9 5AG, Northern Ireland.

(*Received in UK* 18 *December* 1989)

Abstract Condensation of cyclic secondary α- amino esters with aryl aldehydes containing an ω-alkenyl group leads to intramolecular 1,3-dipolar cycloaddition, via an intermediate azomethine ylide, in good yield. The stereochemistry of the azomethine ylides is controlled by steric interactions developing during conversion of the intermediate carbinolamines to the iminium ion species and generally results in stereo specific dipole formation. There is no pronounced endo - exo selectivity in these cycloadditions and an intramolecular β-acrylate moiety is a more reactive dipolarophile than an intermolecular maleimide moiety.

Azomethine ylides are readily available from both α-amino acids and their esters via imine formation(1).[2] Imine formation results in activation of bonds a and b in the imine (1) and leads to azomethine ylides either by 1,2-prototropy (1) ⇄ (2)[3] or by decarboxylation (1) → (3).[4,5] These reactions provide excellent *in vitro* analogues of biochemical processes mediated by pyridoxal racemases[6] and by pyridoxal and pyruvate dependent decarboxylases.[7,8] The regio- and stereo-selectivity of 1,3-dipolar cycloaddition reactions have resulted in many elegant applications of their intramolecular cycloaddition reactions.[9] Some ten years ago we reported on the intramolecular cycloaddition reactions of azomethine ylides formed by the 1,2-prototropy route from primary α-amino esters[10] and recently we provided biochemically relevant examples involving pyridoxal imines.[11] Subsequently we reported on the stereochemistry and mechanism of analogous intramolecular cycloaddition processes involving the decarboxylative route to azomethine ylides.[12]

Imines of secondary α-amino acids and their esters react analogously to give azomethine ylides via deprotonation of intermediate iminium species. However, apart from several examples reported by Confalone et al.,[13] who applied the methodology to the synthesis of Sceletium alkaloid A_4, there has not been a systematic study of the intramolecular cycloaddition of azomethine ylides generated from cyclic secondary α-amino esters and carbonyl compounds. We now report the results of such a study.

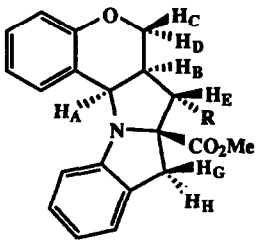


There are two approaches to intramolecular cycloaddition of azomethine ylides generated from secondary α-amino esters and carbonyl compounds. The dipolarophile can be incorporated into either the α-amino ester moiety or the carbonyl component. Our studies have employed the latter approach. Thus aldehydes (4a-c) were reacted with a slight excess (1.2 mol) of secondary α-amino esters (5), 6(a-c), (7) and (8a, b) in boiling toluene over 24-48h.[14] Typically the reactions went to ca. 80% conversion in the case of (5) after 48h whereas the other α-amino esters reacted completely after 24h. The nature of the products is a function of the structure of both the secondary α-amino ester and the carbonyl component/dipolarophile (4a-c).

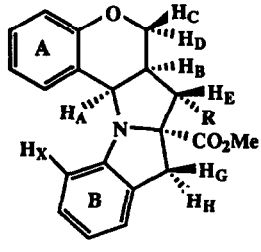
Cycloadditions of Methyl Indoline-2-carboxylate(5)

Aldehyde (4a) reacts with (5) to give a 1.2:1 mixture (75%) of cycloadducts (9a) and (10a) derived from the anti- (11)- and syn- (12)-dipoles respectively (anti and syn refer to the relative configuration of the 1,3- H/CO_2Me dipole substituents). The analogous reaction of (4b) with (5) affords a 1:2 mixture (55%) of (9b) and (10b). In contrast (4c) reacts with (5) to give a single cycloadduct (14)(48%) derived solely from the syn-dipole (12). The assignment of stereochemistry to the cycloadducts (9), (10), and (14) by ^{1}H n.m.r. was complicated by the presence of the carbomethoxy group at the ring junction. The ^{1}H - n.m.r. spectrum of one isomer of each pair of stereoisomers, i.e. (10a) and (10b), showed unusual features in that one aromatic proton and one of the protons of the

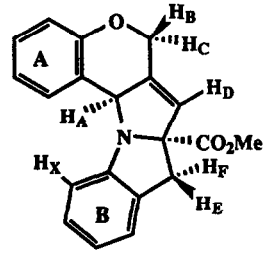
methylene group adjacent to oxygen were substantially shielded and occurred at ca. δ5.7 and ca. δ3.1 respectively. Model building suggested there were several possible stereochemical explanations for these effects. The structures of (9a) and (10b) were therefore determined by single crystal X-ray structure analysis (see experimental section). Due to problems with crystallisation it was not possible to determine structures of one pair of isomers. Projections of (9a) and (10b) derived from the crystal data are shown in Figures 1 and 2 respectively. The X-ray data provide an immediate explanation for the unusual shielding effects observed in the ^{1}H n.m.r. spectra of (10a) and (10b). Thus H_X in (10b) is located close to the π-cloud of ring A whilst H_C is similarly shielded by ring B. The distances between H_X and H_C and the planes of the two aromatic rings are 3.17 A and 3.29 A respectively. The closest approach of H_X to a ring A carbon atom is 2.64 A and of H_C to a ring B carbon atom is 2.51 A. Cycloadduct (14) also shows substantial, though reduced, shielding of H_X (δ 6.01). In this case incorporation of the double bond into the pyrrolidine ring results in conformational changes that remove H_B from the proximity of the π-cloud of ring B and increase the distance of H_X from the plane of ring A.



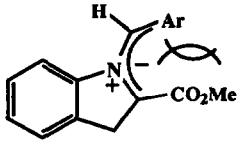
(9) a. R= CO_2Me
b. R= H_F



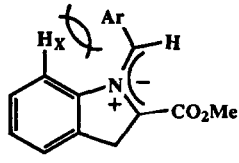
(10) a. R= CO_2Me
b. R= H_F



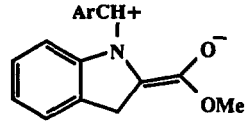
(14)



(11)



(12)



(13)

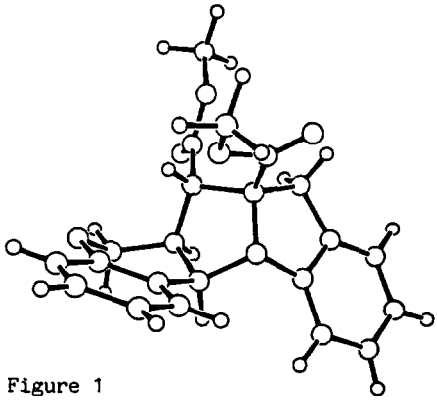


Figure 1

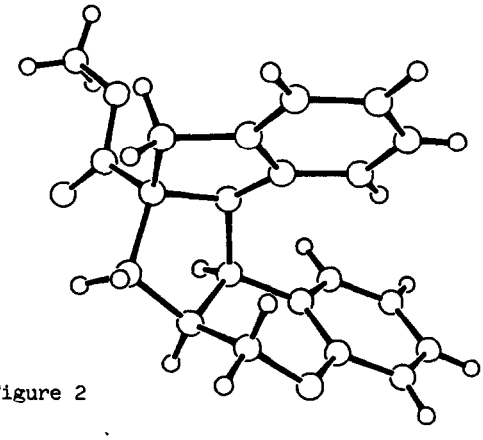
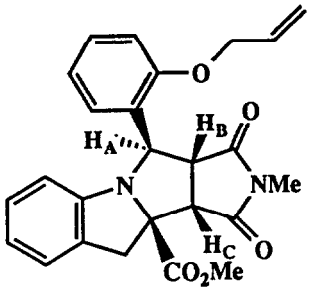


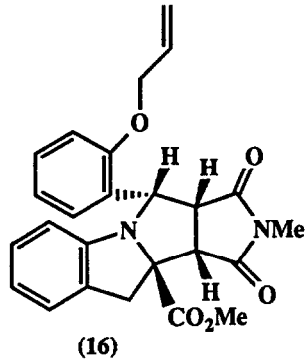
Figure 2

The variation in the product ratio arising from the two dipoles (11) and (12) suggested dipole equilibration was occurring, at least in the case of cycloadditions involving (4b) and (4c), and that the product ratios reflect the relative transition state energies, i.e. cycloaddition is slower than dipole equilibration when the dipolarophile is non-activated. This has been previously established for cycloadditions involving stabilised azomethine ylides derived from primary α-amino esters[10] and non-stabilised azomethine ylides derived via the decarboxylative route.[12] To assess the dipole distribution produced under kinetic control we studied the reaction of (4b) with (5) and N-methylmaleimide (NMM). Extensive experience with maleimide dipolarophiles has shown that, due to their high reactivity, they trap the dipole(s) produced under kinetic control and do not permit dipole equilibration.[10,15]

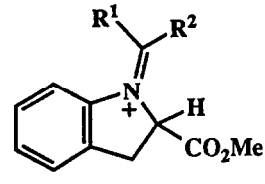
The reaction of (4b), (5) and NMM (toluene, 100°C, 48h) afforded a 1.3:1 mixture (70%) of (15) and (16). Once again the presence of the angular cabomethoxy group in (15) and (16) rendered stereochemical assignments by ^{1}H n.m.r. difficult. Moreover, (16) gave a partially broadened ^{1}H n.m.r. spectrum due to conformational mobility of the aryloxy moiety. The stereochemistry of (15) and (16) were accordingly determined by single crystal X-ray structure analysis (see experimental section). Projections of (15) and (16) derived from the X-ray data are shown in Figures 3 and 4 respectively.



(15)



(16)



(17) a. R^1= H, R^2= Ar
b. R^1= Ar, R^2= H

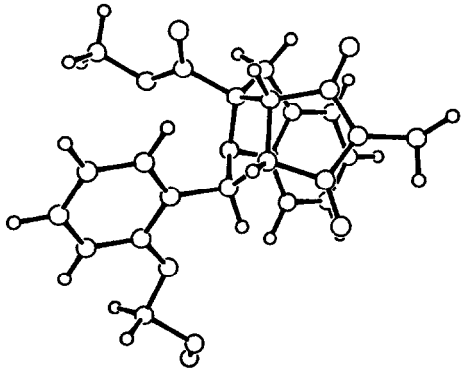


Figure 3

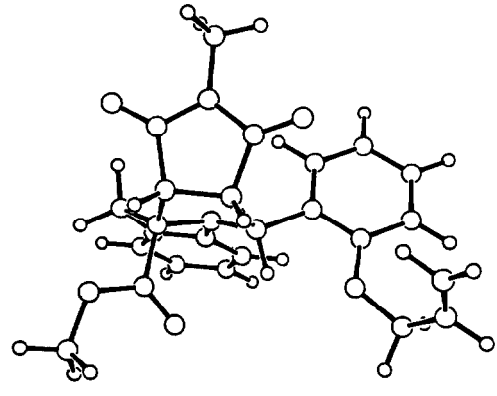


Figure 4

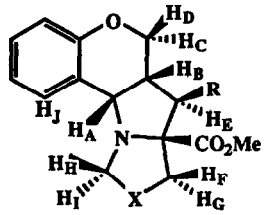
It is clear from the ratio of (15) to (16) that kinetically controlled dipole formation from (5) is non-stereospecific unlike the situation in primary amino esters.[15] Both dipoles (11) and (12) contain a severe sterically destabilising interaction, Ar/CO_2Me in (11) and Ar/H_x in (12). These dipoles also lack the potential for hydrogen-bonding believed to be important in kinetically controlled formation of (2).[15,17] Moreover, the ortho-alkyloxy substituent results in a greater contribution of canonical forms such as (13) to the dipole resonance hybrid which, in turn, assist stereomutation (11) ⇄ (12) in cases where cycloaddition is rate limiting, by lowering the barrier to rotation about the ArCH-N bond. In contrast, azomethine ylides (2) undergo significant stereomutation only when they possess 1,3-diaryl substituents (R and R^2 = aryl).[10,15] Non-stereospecific dipole formation from (5) and aryl aldehydes is due to the steric interactions referred to above which manifest their effects in the carbinolamine → iminium ion step. Thus formation of the iminium ions (17a) and (17b) is believed to be slow. Subsequently rapid deprotonation then affords (11) and (12). π-Overlap of the aryl group with the dipole moiety is substantially reduced in both dipoles due to the twisting necessary to relieve the steric interactions. The formation of (14) as the sole product from (5) and (4c) parallels the result obtained with analogous cycloadditions involving non-stabilised azomethine ylides generated by the decarboxylative route[12] and appears to result from a more favourable alignment of the four reacting centres in dipole (12), i.e. kinetically controlled selection of (12) from an equilibrating mixture of (11) and (12).

The question of relative rates of dipole formation and cycloaddition in the reaction of (4a) with (5) was probed by repeating the reaction in the presence of 1 mol of NMM. This reaction resulted in the same mixture of cycloadducts, (9a) and (10a), as were observed in the absence of NMM and no NMM cycloadducts were observed. Thus in this case the intramolecular cycloaddition is fast and the product ratio reflects the dipole mixture produced under kinetic control.

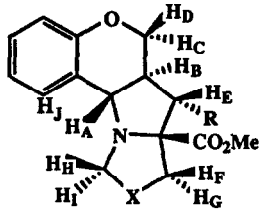
One final point deserves comment. The reaction of the free carboxylic acid derivative of (5) with aryl aldehydes occurs with decarboxylation and produces non-stabilised azomethine ylides which undergo 1,4-prototropy to give indoles.[18] No indoles are observed in the case of the stabilised ylides (11) and (12) reflecting the reduced tendency of these ylides to protonate at the benzylic carbon centre of the dipole moiety.

Cycloaddition of the Monocyclic Secondary α-Amino Esters (6a-c)

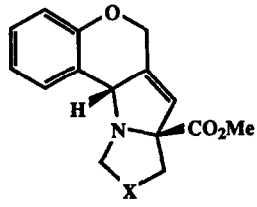
The importance of steric interactions in controlling the stereochemistry of azomethine ylides derived from cyclic secondary α-amino esters is apparent when the α-amino esters (6a-c) are reacted (toluene, 110°C) with the aldehydes (4a-c). Although aldehydes (4a) and (4b) give rise to two cycloadducts (18) and (19) in each case (Table 1) whilst (4c) affords a single cycloadduct (20), in all cases the cycloadducts are derived from the syn-dipole (21). Stereospecific formation of syn-dipole (21) has been observed in related inter- and intra-molecular cycloaddition reactions of azomethine ylides derived from proline and pipecoline esters.[13,19]



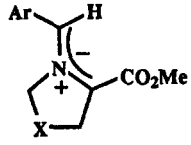
(18) a. R= CO_2Me, X= CH_2
b. R= CO_2Me, X= $(CH_2)_2$
c. R= CO_2Me, X= S
d. R= H, X= $(CH_2)_2$
e. R= H, X= S



(19) a. R= CO_2Me, X= CH_2
b. R= CO_2Me, X= $(CH_2)_2$
c. R= CO_2Me, X= S
d. R= H, X= $(CH_2)_2$
e. R= H, X= S



(20) a. X= $(CH_2)_2$
b. X= S



(21)

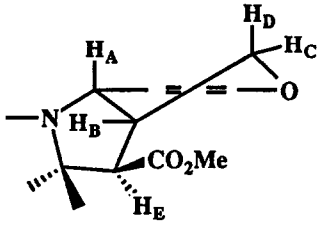
Table 1 Cycloadducts derived from the reaction of (4a-c) with (6a-c) in boiling toluene over 24h.

Amino ester	Aldehyde	Product(s)(ratio)[a]	Yield(%)[b]
6a	4a	18a(1), 19a(4.6)	86
6b	4a	18b(1), 19b(1.5)	87
6c	4a	18c(1), 19c(1)	60
6b	4b	18d(3.3), 19d(1)	80[c]
6c	4b	18e(4), 19e(1)	60
6b	4c	20a	67
6c	4c	20b	46

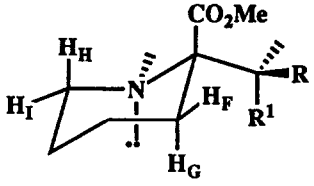
a. Product ratio calculated from the ^1H n.m.r. spectrum of the reaction mixture.
b. Isolated yields.
c. Reference 13 reports a 10:1 ratio of (18d) to (19d) for the ethyl ester.

The ring junction stereochemistry of (18) and (19) was readily established on the basis of both coupling constants (cis $J_{H_AH_B}$ 6.5-9.3 Hz, trans $J_{H_AH_B}$ 10.6-12.2 Hz) and n.O.e studies. Typical ^1H n.m.r. studies are described for (18b) and (19b) as a representative pair of isomers. The ^1H n.m.r. spectrum ($CDCl_3$) of (18b) exhibits a signal for H_A at δ 4.31 (d, J_{AB} 8.9 Hz). The coupling constants in the pyran ring suggest a cis ring junction with a half chair conformation(22) for the pyran ring (J_{BC} 1.4 Hz and J_{BD} 3.4 Hz) Protons H_E(d) and H_B(m) have similar chemical shifts (δ 3.05) and are

only just separated at 400 MHz. Positive n.O.e's are observed from H_E to H_G, H_I to H_J (aromatic proton), and H_B to H_A, H_C and H_D. These n.O.e's are consistent with a chair conformation for the piperidine ring(23a).

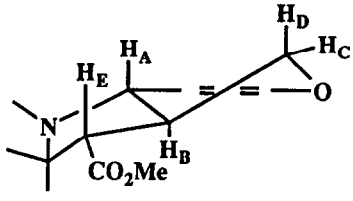


(22)

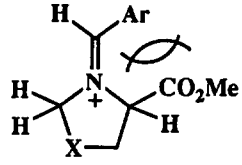


(23) a. R= CO_2Me, R^1= H_E
b. R= H_E, R^1= CO_2Me

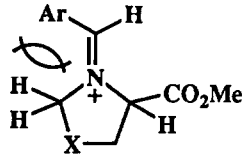
In the ^1H n.m.r. spectrum ($CDCl_3$) of cycloadduct (19b) the ring junction proton H_A gives rise to a doublet (J_{AB} 10.6 Hz) at δ4.15. The large coupling constants J_{AB}, J_{BD}(11.4 Hz) and J_{BE} (10.1Hz) together with a small coupling constant for J_{BC} (4.7 Hz) demonstrates that H_B is trans diaxial to H_A and H_D(24). N.O.e studies($CDCl_3$) show positive n.O.e's from H_E to H_A and H_D and from H_H/H_I(δ 3.2, m) to H_J(aromatic). The signal for H_F(δ2.14) is distinguishable, but that for H_G overlaps with those of the other piperidine methylene protons(δ 1.4-1.75). However, addition of C_6D_6 allows this signal to be resolved and further n.O.e. studies show no n.O.e. from H_G to H_E suggesting a trans-relationship(23b). Small n.O.e's are observed from H_A to H_H/H_I and a large n.O.e. is observed from H_D to H_A.



(24)



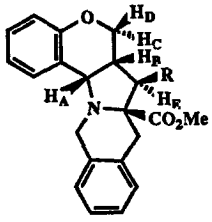
(25)



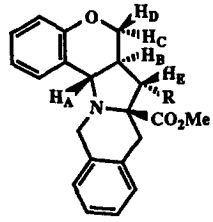
(26)

The stereospecific formation of syn-dipole(21) arises from the developing steric interaction between the aryl group and the flanking $CHCO_2Me$(25) or CH_2(26) group in conversion of the intermediate carbinolamine into these iminium ion species. The former is subject to substantially more steric interaction than the latter although even in (26) the plane of the aryl group must be twisted significantly out of the plane of the iminium moiety reducing delocalisation in the transition state. Dipole formation is then completed by a fast deprotonation of (26). A study of molecular models shows the transition states leading to both (18) and (19) involve substantial twisting of the aryl moiety with consequent loss of π-overlap. The predominance of (19a) over (18a) appears to be steric in origin with the ester group on the dipolarophile experiencing less steric hindrance in the endo-transition state.

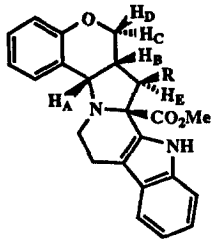
Cycloadditions to Tetrahydroisoquinoline- and Tetrahydro-β-Carboline-α-Amino Esters. (7) and (8a,b). Reactions (toluene 110°C) of the α-amino esters (7), (8a) and (8b) with the aldehydes (4a-c) paralleled the results of the foregoing section with monocyclic α-amino esters. Reactions with aldehydes (4a) and (4b) gives rise to two cycloadducts (27)-(32) in each case both of which are derived from a dipole with the same configuration [analogous to (21)], via endo- and exo- transition states. Aldehyde(4c) gives a single cycloadduct, (33)-(35), in each case, which are again derived from dipoles analogous to (21). Isomer ratios and yields are collected in Table 2.



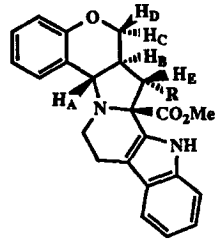
(27) a. R= CO_2Me
b. R= H



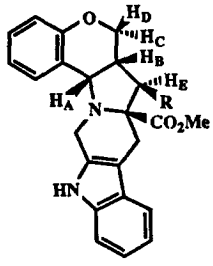
(28) a. R= CO_2Me
b. R= H



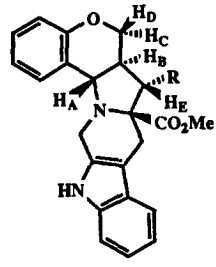
(29) a. R= CO_2Me
b. R= H_F



(30) a. R= CO_2Me
b. R= H_F

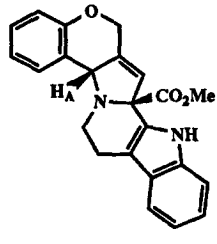


(31) a. R= CO_2Me
b. R= H_F

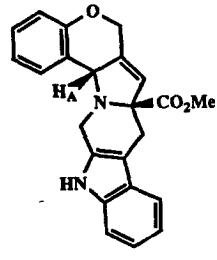


(32) a. R= CO_2Me
b. R= H_F

(33)



(34)



(35)

Table 2 Cycloadducts derived from the reaction of (4a-c) with α-amino esters(7), (8a) and (8b) in boiling toluene over 24h.

Amino ester	Aldehyde	Product(s)(ratio)[a]	Yield(%)[b]
7	4a	27a(1.7), 28a(1)	82
8a	4a	29a(1), 30a(1.5)	80
8b	4a	31a(1), 32a(2.2)	63
7	4b	27b(3.2), 28b(1)	72
8a	4b	29b(5), 30b(1)	85
8b	4b	31b(1.2), 32b(1)	45
7	4c	33	67
8a	4c	34	85
8b	4c	35	30

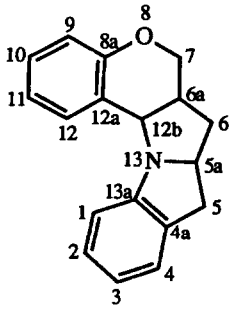
a. Product ratio calculated from the ^{1}H n.m.r. spectrum of the reaction mixture.

b. Isolated yield

Dipole Stereochemistry and Endo-Exo Cycloaddition Stereoselectivity. The results of our studies reported in this paper show that for the reaction of cyclic secondary α-amino esters with aryl aldehydes the stereochemistry of the derived azomethine ylide is controlled by steric interactions that develop during the conversion of the intermediate carbinolamine to the corresponding iminium ion. In most cases, due to the different steric demand at the two carbon centres flanking the amino group, this leads to stereospecific dipole formation. There is no pronounced endo - exo stereoselectivity in the intramolecular cycloaddition of these dipoles (Tables 1 and 2) and steric factors are mainly responsible for the small stereoselectivities that are observed in some cases.

Experimental General experimental details are as previously noted.[16] Petroleum ether refers to the fraction with b.p. 40-60°C.

General Procedure for Intramolecular Cycloadditions The secondary α-amino ester(3.6 mmol) and the aryl aldehyde(4a-c)(3 mmol) were dissolved in dry toluene (12ml) and boiled under reflux for 24-48h. The reaction mixture was then evaporated to dryness and mixtures of isomers purified by flash chromatography (silica) or by preparative t.l.c.(silica). Isomer ratios and yields are collected in Tables 1 and 2.



5a,6,6aα,12bα-Tetrahydro-5aβ,6α-di(methoxycarbonyl)-6H-chromeno[3′,4′-4,5]pyrrolo[1,2-a] indoline(9a). Colourless rods from methylene chloride-ether, m.p. 200-201°C(Found: C, 69.40; H, 5.7, N, 3.65. $C_{22}H_{21}NO_5$ requires C, 69.65; H, 5.55; N, 3.7%); δ 7.49(d, 1H, ArH), 7.19-7.08(m, 3H, ArH), 6.99-6.79(m, 4H, ArH) 4.72(d, 1H, J 7.6 Hz, H_A), 4.33(dd, 1H, J 2.0 and 12 Hz, Hc), 4.24(d, 1H, J 11.3Hz, H_E), 4.22(dd, 1H, J 2.1 and 11.8 Hz, H_D), 3.73(s, 3H, OMe), 3.60(d, 1H, J 17 Hz, H_G), 3.38(s, 3H, OMe), 3.11(d, 1H, H_H) and 2.94(m, 1H, H_B); m/z(%) 379(M^+, 43) 320(89), 203(20), 188(100), 144(6) and 131(13).

5a,6,6aα,12bα-Tetrahydro-5aα,6α-di(methoxycarbonyl)-6H-chromeno[3′4′-4,5] pyrrolo[1,2-a] indoline(10a) Colourless thick oil (Found: C, 69.85; H, 5.5; N, 3.75%); δ 7.66 and 7.29(2xm, 2x1H, ArH), 7.04(m, 2H, ArH), 6.92(d, 1H, ArH), 6.70(m, 2H, ArH), 5.71(m, 1H, ArH), 5.01(d, 1H, J 6.2 Hz, H_A), 4.11(m, 1H, H_D), 3.81 and 3.75(2 x s, 2 x 3H, OMe), 3.68 and 3.46(2 x d, 2 x 1H, J 16.5Hz, H_H and H_G), 3.19(m, 1H, H_B), 3.10(dd, 1H, J 11.3 and 9,7 Hz) and 2.72(d, 1H, J 5.0Hz, H_E); m/z(%) 379(M^+, 32), 320(80). 203(19), 188(100), 144(5) and 131(13).

5a,6,6aα,12bα-Tetrahydro-5aβ-methoxycarbonyl-6H-chromeno[3′,4′-4,5]pyrrolo[1,2-a]indoline(9b) Colourless plates from methylene chloride-ether, m.p. 145-146°C(Found: C, 74.20; H, 5.9; N, 4.65. $C_{20}H_{19}NO_3$ requires C, 74.75; H, 5.95; N, 4.35 %); δ 7.66(dd, 1H, ArH), 7.16(m, 3H, ArH), 6.90(m, 4H, ArH), 4.71(d, 1H, J 7.8Hz, H_A), 4.16(dd, 1H, J 11.5 and 3.3Hz, H_C), 4.02(dd, 1H, J 11.5 and 4.4Hz, H_D), 3.42(d, 1H, J 16.3Hz, H_G), 3.34(s, 3H, OMe), 3.26(d, 1H, H_H), 2.87(dd, 1H, J 13.4 and 7.5 Hz, H_E), 2.67(m, 1H, H_B) and 2.09(dd, 1H, J 13.4 and 9.6Hz, H_F); m/z(%) 321(M^+,25), 262(100) 145(96), 131(17) and 130(20).

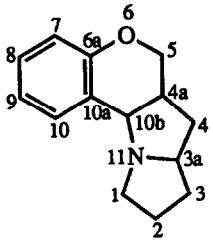
5a,6,6aα,12bα-Tetrahydro-5aα-methoxycarbonyl-6H-chromeno[3′,4′-4,5]pyrrolo[1,2-a]indoline(10b) Colourless prisms from ether-petroleum ether, m.p. 111-112°C(Found: C, 74.25; H, 6.5; N, 4.25%); δ 7.69(d, 1H, ArH), 7.28(m, 1H, ArH), 7.01(m, 2H, ArH), 6.88(d, 1H, ArH), 6.66 (m, 2H, ArH), 5.66(m, 1H, ArH), 4.72(d, 1H, J 5.5 Hz, H_A), 3.94(dd, 1H, J 10.9 and 5.5 Hz, H_D), 3.83(s, 3H, OMe), 3.50 and 3.18(2 x d, 2 x 1H, J 16.1 Hz, H_H and H_G), 3.07(dd, 1H, J 12.1 and 11.5 Hz, H_C), 2.95(dd, 1H, J 14.0 and 8.8 Hz, H_F), 2.55(m, 1H, H_B) and 1.55(dd, 1H, J 14.0 and 2.9 Hz); m/z(%) 321(M^+, 15), 262(59), 175(65), 145(81), 143(100), 130(17), 131(13), 118(22) and 115(51).

5a, 12bα-Dihydro-5aα-methoxycarbonyl-6H-chromeno[3′,4′-4,5]pyrrolo[1,2-a]indoline(14) Colourless rods from methanol, m.p. 182-183°C(Found: C, 75.05; H, 5.65; N, 4.05. $C_{20}H_{17}NO_3$ requires C, 75.2; H, 5.35; N, 4.4%); δ 7.81(d, 1H, ArH), 7.24(m, 1H, ArH), 7.06(m, 2H, ArH), 6.86(d, 1H, ArH), 6.69(m, 2H, ArH), 6.01(d, 1H, ArH), 5.93(dd, 1H, J 3.0 and 1.6 Hz, H_D), 5.79(d, 1H, J 2.7Hz, H_A), 4.75(d, 1H, J 12.7Hz, H_C), 4.50(dd, 1H, J 12.5 and 1.5Hz, H_B), 3.83(s, 3H, OMe) and 3.41(s, 2H, H_E and H_F); m/z(%) 319(M^+, 7), 260(100), 172(11), 143(9), 130(7), 118(10) and 115(9).

Intermolecular Cycloadducts (15) and (16) (15) Colourless rods from ether - petroleum ether, mp. 147-148°C (Found: C, 69.35; H, 5.55; N, 6.4; $C_{25}H_{24}N_2O_5$ requires C, 69.4; H, 5.6; N, 6.45%); δ7.28 - 6.74(m, 8H, ArH) 6.15(m, 1H, $CH{=}CH_2$), 5.82(s, 1H, H_A), 5.42 and 5.31(2 x d, 2 x 1H, $CH{=}CH_2$), 4.73 and 4.61(2 x dd, 2 x 1H, OCH_2), 4.42 (d, 1H, J 7.9 Hz H_B), 3.94(d, 1H, ArCH). 3.84(d, 1H, J7.9Hz H_C), 3.29(s, 3H, OMe), 3.25(d, 1H, ArCH), 2.45(s, 3H, NMe); m/z(%)(CI-NH_3) 433(M+1, 100),

393(1), 373(3), 332(25) and 176(8).

(16) Colourless needles from ether - petroleum ether, m.p. 174-175°C (Found: C, 69.1; H, 5.55; N, 6.35%); the p.m.r. spectrum of this product was broad; m/z(%)(C]-NH_3) 433(M+1, 100), 393(1), 373(6), 332(27), 272(2) and 176(6).



3a,4,4a,10b-tetrahydro-5H-chromeno[3',4'-4,5]pyrrolo [1,2-a] pyrrolidine skeleton

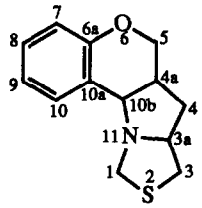
3a,4α,4aβ,10bβ-Tetrahydro-3aβ,4β-di(methoxycarbonyl)-5H-chromeno[3'4'-4,5]pyrrolo[1,2-a]pyrrolidine(18a) and3a,4β,4aα,10bβ-tetrahydro-3aβ,4α-di(methoxycarbonyl)-5H-chromeno[3',4'-4,5]pyrrolo[1,2-a] pyrrolidine(19a) (18a) Thick colourless oil. (Found: C, 65.3; H, 6.4; N, 4.1. $C_{18}H_{21}NO_5$ requires C, 65.25, H, 6.4; N, 4.2%); δ 7.32(dd, 1H, ArH), 7.13(m, 1H, ArH), 6.90(m, 2H, ArH). 4.71(d, 1H, J 9.3Hz, H_A), 4.01(dd, 1H, J 11.4 and 4.4Hz, H_C), 3.92(dd, 1H, J 11.4 and 4.6Hz, H_D), 3.73 and 3.75(2 x s, 2 x 3H, OMe), 3.33(m, 1H, H_B), 2.92(d, 1H, J 9.7Hz, H_E), 2.61, 2.52, 2.29 and 2.10(4 x m, 4 x 1H, H_F, H_G, H_H and H_I), and 1.72-1.91(m, 2H, CH_2); m/z(%)(C]-NH_3) 322(M+1, 100) 272(23), 142(2) and 131(1).

(19a) Colourless plates from methylene chloride-ether, m.p. 116-117°C(Found: C, 65.3; H, 6.4; N, 4.15. $C_{18}H_{21}NO_5$ requires C, 65.25; H, 6.4; N, 4.2%); δ 7.32(dd, 1H, ArH), 7.11(m, 1H, ArH), 6.84(m, 2H, ArH), 4.64(dd, 1H, J 10.1 and 3.9Hz, H_C), 4.14(d, 1H, J 11.8Hz, H_A), 4.11(dd, 1H, J 10.9 and 10.4Hz, H_D), 3.81 and 3.71(2 x s, 2 x 3H, OMe), 3.47(d, 1H, J 12.0Hz, H_E), 3.23(m, 1H, H_H), 2.59(m, 1H, H_B), and 2.50, 2.31, 1.92, 1.82 and 1.41(5 x m, 5 x 1H, H_I and 2 x CH_2); m/z(%) 331(M^+, 26), 272(100), 212(15), 204(3), 145(5) and 131(8).

1,2,3,4,4a,5α.5aβ,11bβ-Octahydro-4aβ,5β-di(methoxycarbonyl)-6H-chromeno[3',4'-b]indolizine (18b) and 1,2,3,4,4a,5β,5aα,11bβ-Octahydro-4aβ,5α-di(methoxycarbonyl)-6H-chromeno[3',4'-b]indolizine(19b)

(18b) Colourless prisms from methanol, m.p. 89-91°C(Found: C, 66.1; H, 6.75; N, 3.85. $C_{19}H_{23}NO_5$ requires C, 66.05; H, 6.7; N, 4.05%); δ7.16 and 6.94(2 x m, 2 x 2H, ArH), 4.31(d, 1H, J 8.9Hz, H_A), 3.99(dd, 1H, J 11.4 and 1.4Hz, H_C), 3.8(dd, 1H, J 11.5 and 3.4Hz, H_D), 3.72 and 3.68(2 x s, 2 x 3H, OMe), 3.05(m, 2H, H_E and H_B), 2.94 and 2.72(2 x m, 2 x 1H, NCH_2), 2.53(d, 1H, J 12.4Hz, H_F) and 1.65-1.14(m, 5H, H_G and 2 x CH_2), m/z (%) 345(M^+,21), 287(23), 286(100), 227(4), 226(7), 143(3) and 131(5)

(19b) Colourless prisms from methanol, m.p. 95-96°C(Found: C, 66.1; H, 6.8; N, 3.95%); δ 7.37(d, 1H, ArH), 7.13(t, 1H, ArH), 6.87(m, 2H, ArH), 4.42(dd, 1H, J 9.7 and 4.7 Hz, H_c), 4.15(d, 1H, J 10.6 Hz, H_A), 4.07(dd, 1H, J 9.6 and 11.4 Hz, H_D), 3.79 and 3.75(2 x s, 2 x 3H, OMe), 3.20(m, 2H, NCH_2), 3.02(d, 1H, J 10.1 Hz, H_E), 2.92 and 2.14(2 x m, 2 x 1H, H_B and H_F), and 1.75 - 1.40(m, 5H, H_G and 2 x CH_2); m/z (%) 345 (M^+,2), 287(19), 286(100), 227(5), 226(12) and 131(5).



1,3,3a,4a,10b,11-hexahydro-5H-chromeno[3′,4′-b]pyrrolidino[1,5-c]thiazole skeleton.

1,3,3a,4aβ,10bβ,11-Hexahydro-3aβ,4β-di(methoxycarbonyl)-5H-chromeno[3′,4′-b]pyrrolidino[1,5-c]thiazole(18c)and1,3,3a,4aα,10bβ,11-hexahydro-3aβ,4α-di(methoxycarbonyl)-5H-chromeno[3′,4′-b]pyrrolidino[1,5-c]thiazole(19c)

(18c) Thick colourless oil(Found: C, 58.15; H, 5.5; N, 3.85;S, 9.0, $C_{17}H_{19}NO_5$ requires C, 58.45; H, 5.5; N, 4.0; S, 9.17%); δ 7.28(d, 1H, ArH), 7.20(m, 1H, ArH), 6.91(m, 2H, ArH), 4.72(d, 1H, J 8.4Hz, H_A), 4.06(dd, 1H, J 11.4 and 4.2Hz, H_C), 4.0(s, 2H, NCH_2), 3.97(dd, 1H, J 13.2 and 5.7 Hz, H_D), 3.76 and 3.73(2 x s, 2 x 3H, OMe), 3.62(d, 1H, J 11.5 Hz, H_F), 3.31(m, 1H, H_B), 3.12(d, 1H, J 8.2 Hz, H_E) and 3.10(d, 1H, H_G); m/z(%) 349(M^+,4), 291(18), 290(100) and 131(9).

(19c) Colourless prisms from methylene chloride-ether, m.p. 158-160°C(Found: C, 58.15; H, 5.5; N, 3.85; S, 9.0%); δ 7.32(d, 1H, ArH), 7.16(m, 1H, ArH), 6.90(m, 2H, ArH), 4.64(dd, 1H, J 10.2 and 3.9 Hz, H_C), 4.29(d, 1H, J 12.2 Hz, H_A), 4.24(d, 1H, J 9.5Hz, H_H), 4.04(t, 1H, J 10.7Hz, H_D), 3.88(d, 1H, H_I), 3.85 and 3.76(2 x s, 2 x 3H, OMe), 3.65(d, 1H, J 12.7 Hz, H_F), 3.47(d, 1H, J 11.9 H_z, H_E), 3.03(d, 1H, H_G) and 2.82(m, 1H, H_B); m/z(%) 349(M^+,34), 290(100), 188(75), 161(53), 147(12), 145(12), 132(13) and 131(33).

1,2,3,4,4a,5,5aβ,11bβ-Octahydro-4aβ-methoxycarbonyl-6H-chromeno[3′,4′-b]indolizine(18d) and 1,2,3,4,4a,5,5aα,11bβ-octahydro-4aβ-methoxycarbonyl-6H-chromeno[3′,4′-b]indolizine(19d)

(18d) Colourless thick oil(Found: C, 69.8; H, 7.3; N, 5.0. $C_{17}H_{21}NO_3$ 0.05 mol $CHCl_3$ requires C, 69.81; H, 7.23; N, 4.77%) δ 7.20-6.89(m, 4H, ArH), 4.14(d, 1H, J6.5Hz, H_A), 3.85(m, 2H, OCH_2), 3.73(s, 3H, OMe), 2.97(m, 2H, NCH_2), 2.40-2.27(m, 3H, H_B, H_E and H_F), and 1.57 and 1.22(2 x m, 2 x 3H, 3 x CH_2); m/z(%) 287(M^+,0.5) 229(17), 228(100), 145(2) and 131(6)

(19d) Colourless thick oil(Found: C, 69.80; H, 7.30; N, 5.0%) δ 7.39-6.80(m, 4H, ArH), 4.45(dd, 1H, J 9.6 amd 4.7Hz, H_C), 4.09(dd, 1H, J 9.6 and 11.9Hz, H_D), 4.03(d, 1H, J11.9Hz, H_A), 3.74(s, 3H, OMe), 3.23 and 3.0(2 x m, 2 x 1H, NCH_2), 2.43(m, 1H, H_B), 2.28(m, 1H), 2.03(dd, 1H, J13.8 and 10.0Hz, H_E), 1.90(dd, 1H, J13.8 and 9.4Hz, H_F), 1.67(m,3H) and 1.47 and 1.27(2 x m, 2 x 1H); m/z(%) 287(M^+,25), 229(16) 228(100), 145(3) and 131(6).

1,3,3a,4aβ,10bβ,11-Hexahydro-3aβ-methoxycarbonyl-5H-chromeno[3′,4′-b]ipyrrolidino[1,5-c]thiazole(18e)and 1,3,3a,4aα,10bβ,11-hexahydro-3aβ-methoxycarbonyl-5H-chromeno[3′,4′-b]ipyrrolidino[1,5-c]thiazole(19e)

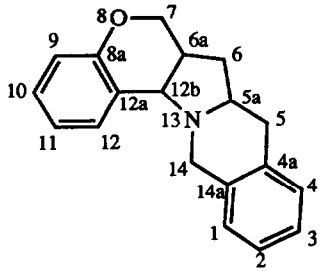
(18e) Thick colourless oil [Found: (mixed isomers) N, 4.75. $C_{15}H_{17}NO_3S$ requires N, 4.8%]; δ 7.35(d, 1H, ArH), 7.19(m, 1H, ArH), 6.91(m, 2H, ArH), 4.57(d, 1H, J6.7Hz, H_A), 4.16(s, 2H, NCH_2), 4.02(dd, 1H, J10.8 and 4.1Hz, H_C), 3.91(dd, 1H, J11.1 and 8.0Hz, H_D), 3.78(s, 3H, OMe), 3.46(d, 1H, J11.2Hz, H_F), 2.74(m, 1H, H_B), 2.72(d, 1H, H_G), 2.65(dd, 1H, J13.1 and 9.2Hz) and 1.91(dd, 1H, J13.1 and 4.4Hz, H_E); m/z(%) 291(M^+,4),232(100), 186(10), 145(6) and 131(13).

(19e) It did not prove possible to isolate the minor isomer in pure form. The p.m.r. spectrum of the

mixture gave incomplete data for (19e) due to overlap of signals. δ 4.53(dd, 1H, J10.1 and 4.1 Hz, H_D), 4.29(d, 1H, J9.4Hz, H_A), 3.68 and 3.08 (2 x d, 2 x 1H, H_F + H_G) and 2.07(dd, 1H, J10.6 and 9.0Hz).

1,2,3,4,4a,11bβ-Hexahydro-4aβ-methoxycarbonyl-6H-chromeno[3′,4′-b]indolizine(20a) Colourless plates from methanol, m.p. 95-97°C(Found: C, 71.0; H, 6.65; N, 4.75. $C_{17}H_{19}NO_3$ requires C, 71.55; H, 6.7; N, 4.9%); δ 7.4(d, 1H, ArH), 7.16(m, 1H, ArH), 6.92(m, 2H, ArH), 5.81(s, 1H, C=CH), 5.10(s, 1H, H_A), 4.67 and 4.55 (2 xd, 2 x 1H, J12.7Hz, OCH_2), 3.72(s, 3H, OMe), 3.27(m, 2H, NCH_2), 2.33(m, 1H), and 1.74-1.18(m, 5H); m/z(%) 285(M^+,2), 227(36) and 226(100).

1,3,3a,10bβ-Tetrahydro-3aβ-methoxycarbonyl-5H-chromeno[3′,4′-b]pyrrolo[1,5-c]thiazole(20b) Thick colourless oil(Found: N, 4.5. $C_{15}H_{15}NO_3S$ requires N, 4.85%); δ 7.36(d, 1H, ArH), 7.10 and 6.91(2 x t, 2 x 1H, ArH), 6.82(d, 1H, ArH), 5.77 (s, 1H, C=CH), 5.39(s, 1H, H_A), 4.82 and 4.55(2 x d, 2 x 1H, SCH_2N), 4.01 and 3.91(2 x d, 2 x 1H, OCH_2), 3.82 (s, 3H, OMe), and 3.55 and 3.18(2 x d, 2 x 1H, SCH_2); m/z(%) 289(M^+,2), 230(100) and 184(16).



5,5a,6,6a,12b,14-hexahydro-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline skeleton

5,5a,6α,6aβ,12bβ,14-Hexahydro-5aβ,6β-di(methoxycarbonyl)-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline(27a) and 5,5a,6β,6aα,12bβ,14-hexahydro-5aβ,6α-di(methoxycarbonyl)-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline(28a)

(27a) Colourless rods from ether-petroleum ether, m.p. 122-124°C(Found: C, 69.9; H, 5.75; N, 3.45. $C_{23}H_{23}NO_5$ requires C, 70.2; H, 5.9; N, 3.55%); δ 7.20(m, 2H, ArH), 7.0(m, 6H, ArH), 4.34(d, 1H, J8.9Hz, H_A), 4.13(d, 1H, J11.4Hz, H_C), 4.04 and 3.94(2 x d, 2 x 1H, NCH_2), 3.90(dd, 1H, J11.7 and 3.0Hz, H_D), 3.79(s, 3H, OMe), 3.64(d, 1H, J15.5Hz, ArCH), 3.55(s, 3H, OMe), 3.27(m, 2H, H_B + H_E), and 2.93(d, 1H, ArCH); m/z(%) 393(M^+,1), 334(100) 262(7), 261(9), 203(2), 202(5), 189(1), 188(1), 130(4) and 129(2).

(28a) Colourless rods from ether-petroleum ether, m.p. 174-175°C(Found: C, 69.9; H, 5.8; N, 3.45%); δ 7.46(d, 1H, ArH), 7.18-6.87(m, 7H, ArH), 4.51(dd, 1H, J9.9 and 4.3 Hz, H_C), 4.41(d, 1H, J 11.4 Hz, H_A), 4.27 and 4.16(2 x d, 2 x 1H, NCH_2), 4.10(dd, 1H, J 10.1 and 11.3 Hz, H_D), 3.78 and 3.66(2 x s, 2 x 3H, OMe), 3.30(d, 1H, $ArCH_2$), 3.25(d, 1H, J 11.8 Hz, H_E), 2.92(d, 1H, $ArCH_2$), 2.82(m, 1H, H_B); m/z(%) 393(M^+,9), 334(100), 228(20) 274(21), 256(14), 188(11), 167(9), and 131(7)

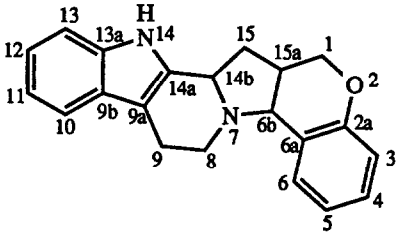
5,5a,6,6aβ,12bβ,14-Hexahydro-5aβ-methoxycarbonyl-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline(27b) and5,5a,6,6aα,12bβ,14-hexahydro-5aβ-methoxycarbonyl-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline(28b)

(27b) Colourless plates from methylene chloride-ether, m.p. 150-152°C(Found: C, 75.2; H, 6.35; N, 3.9.

$C_{21}H_{21}NO_3$ requires C, 75.2, H, 6.3; N, 4.15%); δ 7.30 and 7.17(2 x m, 2 x 1H, ArH), 7.0(m, 6H, ArH), 4.31(d, 1H, J 6.7Hz, H_A), 4.23 and 4.12(2 x d, 2 x 1H, J 14.6Hz, NCH_2), 3.99(dd, 1H, J 10.7 and 8.1Hz, H_D), 3.92(dd, 1H, J10.7 and 4.9Hz, H_C), 3.57(s, 3H, OMe), 3.47 and 2.77(2 x d, 2 x 1H, J 15.2 Hz, $ArCH_2$), 2.60(m, 1H, H_B), and 2.47 amd 1.72(2 x dd, 2 x 1H, CH_2); m/z(%) 335(M^+,2), 274(44), 276(100), 203(5), 145(10), 144(9), 131(8) and 130(5).

(28b) Colourless prisms from ether-petroleum ether, m.p. 135-137°C(Found: C, 75.2; H, 6.35; N, 3.9%); δ 7.50(d, 1H, ArH), 7.11(m, 4H, ArH), 6.89(m, 3H, ArH), 4.44(dd, 1H, J10.0 and 4.3Hz, H_C), 4.25(m, 3H, H_A and NCH_2), 4.06(dd, 1H, J 10.1 and 11.5Hz, H_D), 3.65(s, 3H, OMe), 3.47 and 2.98(2 x d, 2 x 1H, J 14.9Hz, $ArCH_2$), 2.23(m, 1H, H_B), 2.04 and 1.94(2 x dd, 2 x 1H, CH_2); m/z(%) 335(M^+,18), 276(100), 230(42), 145(14) and 131(17).

5,5a,12bβ,14-Tetrahydro-5aβ-carbomethoxy-7H-chromeno[3′,4′-4,5]pyrrolo[1,2-b]isoquinoline(33) Colourless rods from methylene chloride-ether, m.p. 180-181°C(Found: C, 75.45; H, 5.7; N, 4.0. $C_{21}H_{19}NO_3$ requires C, 75.65; H, 6.75; N, 4.2%); δ 7.44(d, 1H, ArH), 7.17(m, 5H, ArH), 6.93(m, 2H, ArH), 5.97(s, 1H, C=CH), 5.23(s, 1H, H_A), 4.74 and 4.61(2 x d, 2 x 1H, J12.5, OCH_2), 4.54(d, 2H, NCH_2), 3.58(s, 3H, OMe), and 3.49 and 3.04(2 x d, 2 x 1H, J 14.8 Hz, $ArCH_2$); m/z(%) 333(M^+,1), 275(21) and 274(100).



6b,8,9,14b,15,15a-hexahydro-1H-chromeno[3′,4′-2,3]indolizino[6,7-b]indole skeleton

6bβ,8,9,14b,15α,15aβ-Hexahydro-14bβ,15β-di(methoxycarbonyl)-1H-chromeno[3′,4′-2,3]indolizino[6,7-b]indole(29a) and 6bβ,8,9,14b,15β,15aα-hexahydro-14bβ,15α-di(methoxycarbonyl)-1H-chromeno[3′,4′-2,3]indolizino[6,7-b]indole(30a)

(29a) Colourless rods from methylene chloride-ether, m.p. 186-187°C(Found: C, 69.6; H, 5.7; N, 6.25. $C_{25}H_{24}N_2O_5$ requires C, 69.4; H, 5.6; N, 6.45%); δ 9.26(s, 1H, NH), 7.44, 7.41(2 x d, 2 x 1H, ArH), 7.36-6.99(m, 6H, ArH), 4.17(d, 1H, J 8.4Hz, H_A), 4.07 and 3.98(2 x dd, 2 x 1H, J 11.4 and 4.4 Hz, OCH_2), 3.92 and 3.66(2 x s, 2 x 3H, OMe), 3.39(m, 1H, H_B), 3.24(m, 1H, NCH), 3.22(d, 1H, J 7.9Hz, $C\underline{H}CO_2Me$), 3.07(m, 1H, NCH), and 2.63(m, 2H, CH_2); m/z(%) 432(M^+,2), 373(100), 313(6), 154(4) and 131(8)

(30a) Colourless plates from methylene chloride-ether, m.p. 215-216°C(Found: C, 69.3; H, 5.75; N, 6.25%); δ 8.13(s, 1H, NH), 7.51(d, 2H, ArH), 7.32-δ 6.86(m, 6H, ArH), 4.58(dd, 1H, J 10.0 and 3.8 Hz, H_C), 4.15(t, 1H, J 10.7 Hz, H_D), 4.04(d, 1H, J 12.4Hz, H_A), 3.76(s, 3H, OMe), 3.75(d, 1H, J 12.2Hz, H_E), 3.46(m, 1H, H_B), 3.44(s, 3H, OMe), 3.37, 2.97 and 2.78(m, 4H); m/z(%) 432(M^+,10), 373(100), 313(7), 228(11), 168(8) and 131(10).

6bβ,8,9,14b,15,15aβ-Hexahydro-14bβ-methoxycarbonyl-1H-chromeno[3′4′-2,3]indolizino[6,7-b]indole(29b) and 6bβ,8,9,14b,15,15aα-hexahydro-14bβ-methoxycarbonyl-1H-chromeno[3′,4′-2,3]indolizino[6,7-

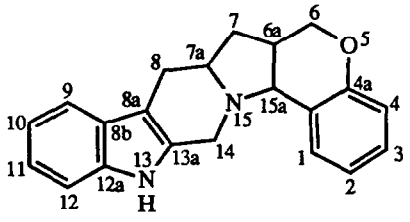
b]indole(30b)

(29b) Colourless plates from methylene chloride-ether, m.p. 188-190° C, which comprise a 4:1 mixture of (29b) and (30b)[Found (mixed isomers): C, 73.55; H, 6.0; N 7.35. $C_{23}H_{22}N_2O_3$ requires C, 73.75; H, 5.9; N, 7.5%]; δ 8.10 (s, 1H, NH), 7.44-6.99(m, 8H, ArH), 4.32(d, 1H, J 6.4Hz, H_A), 3.93(dd, 1H, J10.8 and 4.6Hz, H_C), 3.74(s, 3H, OMe), 3.72(dd, 1H, J10.2 Hz, and 9.1 Hz, H_D), 3.40(m, 2H, NCH_2), 2.82(dd, 1H, J12.7 and 8.2Hz, H_F), 2.57(m, 3H, H_B, CH_2), and 1.91(dd, 1H, J12.7 and 5.0 Hz, H_E); m/z(%) 374(M^+,1), 316(24), 315(100), 157(3) and 131(3).

(30b) Most of the p.m.r. signals of (30b) were obscured by those of the major isomer (29b). δ 8.28 (s, 1H, NH), 4.59(dd, 1H, J10.2 and 4.3Hz, H_C), 4.13(t, 1H, J10.2Hz, H_D) and 4.03(d, 1H, J11.3Hz, H_A).

6bβ,8,9,14b-Tetrahydro-14bβ-methoxycarbonyl-1H-chromeno[3′,4′-2,3]indolizino[6,7-b]indole(34)

Colourless plates from methylene chloride-ether, m.p. 194-195°C(Found: C, 73.95; H, 5.85; N, 7.1. $C_{23}H_{20}N_2O_3$ requires C, 74.15; H, 5.4; N, 7.5%); δ 8.48(s, 1H, NH), 7.55, 7.45 and 7.34(3 x d, 3 x 1H, ArH), 7.12(m, 4H, ArH), 6.89(d, 1H, ArH), 6.14(dd, 1H, J 2.8 and 1.5Hz, C=CH), 5.46(d, 1H, J2.6Hz, H_A), 4.80 and 4.56(2 x d, 2 x 1H, J 12.6Hz, OCH_2), 3.82(s, 3H, OMe), and 2.99, 2.83, 2.59 and 2.40(4 x m, 4 x 1H, NCH_2CH_2); m/z(%) 372(M^+,1), 314(24), 313(100), 157(5) and 141(4).



6a,7,7a,8,14,15a-hexahydro-6H-chromeno[3′,4′-2,3]indolizino[7,8-b]indole skeleton.

6aβ,7α,7a,8,14,15aβ-Hexahydro-7β,7aβ-di(methoxycarbonyl)-6H-chromeno[3′,4′-2,3]indolizino[7,8-b]indole(31a)and6aα,7β,7a,8,14,15aβ-hexahydro-7α,7aβ-di(methoxycarbonyl)-6H-chromeno[3′,4′-2,3]indolizino[7,8-b]indole(32a)

(31a) Colourless plates from methylene chloride-ether, m.p. 240-242°C(Found: C, 69.25; H, 5.55; N, 6.25. $C_{25}H_{24}N_2O_5$ requires C, 69.4; H, 5.6; N, 6.45%); δ 7.79(s, 1H, NH), 7.51, 7.28 and 7.14(3 x m, 3 x 2H, ArH), 4.89 and 4.70(2 x d, 2 x 1H, NCH_2), 4.48(d, 1H, J 10.0Hz, H_A), 4.44(dd, 1H, J 10.2 and 4.6Hz, H_D), 4.16(dd, 1H, J 11.3 and 9.8 Hz, H_C), 3.87 and 3.58(2 x s, 2 x 3H, OMe), 3.44(d, 1H, $ArCH_2$), 3.00(m, 1H, H_B), 2.91(d, 1H, J 10.8 Hz, H_E), 2.80(d, 1H, $ArCH_2$); m/z(%) 432(M^+,10), 373(46), 227(20), 169(27), 143(100) and 131(12).

(32a) Colourless rods from ether-petroleum ether, m.p. 225-227°C(Found: C, 69.25; H, 5.55; N, 6.25. $C_{25}H_{24}N_2O_5$ requires C, 69.4; H, 5.6; N, 4.5%); δ 7.99(s, 1H, NH), 7.50, 7.44 and 7.27(3 x d, 3 x 1H, ArH), 7.26(m, 3H, ArH), 6.96(t, 1H, ArH), 6.87(d, 1H, ArH), 5.12(d, 1H, J 8.7Hz, H_A), 4.33(m, 3H, NCH_2 and H_D), 4.08(dd, 1H, J 11.4 and 3.2Hz, H_C), 3.65(s, 3H, OMe), 3.59(d, 1H, J 7.7Hz, H_E), 3.55(s, 3H, OMe), 3.33 and 3.21(2 x m, 2 x 1H, CH_2) and 2.99(m, 1H, H_B); m/z(%) 432(M^+,8), 373(7), 169(14), 149(10), 143(100) and 131(8).

6aβ,7,7a,8,14,15aβ-Hexahydro-7aβ-methoxycarbonyl-6H-chromeno[3',4'-2,3]indolizino[7,8-b]indole(31b) and 6aα,7,7a,8,14,15aβ-hexahydro-7aβ-methoxycarbonyl-6H-chromeno[3',4'-2,3]indolizino[7,8-b]indole(32b)

(31b) Colourless plates from ether-petroleum ether, m.p. 280-282°C(Found: C, 73.55; H, 5.9; N, 7.3. $C_{23}H_{22}N_2O_3$ requires C, 73.75; H, 5.9; N, 7.5%); δ 7.65(s, 1H, NH), 7.45(d, 1H, ArH), 7.32-6.85(m, 7H, ArH), 4.39 and 4.12(2 x d, 2 x 1H, NCH_2), 4.38(d, 1H, J 7.1Hz, H_A), 4.01(dd, 1H, J 9.8 and 3.5Hz, H_C), 3.66 and 2.66(2 x d, 2 x 1H, $ArCH_2$), 3.58(s, 3H, OMe), 3.56 (d, 1H, J 15.2Hz, H_D), 2.63(m, 1H, H_B), 2.51(dd, 1H, J 12.8 and 8.0Hz, H_F), and 1.89(dd, 1H, J 12.8 and 4.8Hz, H_E); m/z(%) 374(M^+,10), 315(97), 169(25), 143(100), 131(11) and 114(28).

(32b) Colourless rods from methylene chloride-ether, m.p. 246-247°C(Found: C, 73.55; H, 5.9; N 7.3. $C_{23}H_{22}N_2O_3$ requires C, 73.75; H, 5.9; N, 7.5%); δ 7.78(s, 1H, NH), 7.53 and 7.31(2 x d, 2 x 1H, ArH), 7.19(m, 4H, ArH), 6.93(m, 2H, ArH), 4.96(m, 1H, H_A), 4.37(dd, 1H, J 5.9 and 1.8Hz, NCH), 4.25(t, 1H, J 10.7Hz, H_D), 4.10(dd, 1H, J 10.5 and 4.8Hz, H_C), 3.82(d, 1H, J 5.9Hz, NCH), 3.59(s, 3H, OMe), 3.39 and 3.31(2 x m, 2 x 1H, CH_2), 2.47(m, 1H, H_F) and 2.16(m, 2H, H_B and H_E); m/z(%) 374(M^+,89), 315(62), 242(100), 183(39), 169(25), 147(14), 145(11), 132(2) and 131(5).

7a,8,14,15aβ-Tetrahydro-7aβ-methoxycarbonyl-6H-chromeno[3',4'-2,3]indolizino[7,8-b]indole(35)

Colourless rods from methylene chloride-ether, m.p. 243-245°C(Found: C, 73.65; H, 5.3 ; N, 7.4 . $C_{23}H_{20}N_2O_3$ requires C, 74.15; H, 5.4; N, 7.5%); δ 7.78(s, 1H, NH), 7.48, 7.43 and 7.28(3 x 3d, 3 x 1H, ArH), 7.12(m, 3H, ArH), 6.94(m, 2H, ArH), 6.04(s, 1H, C=CH), 5.26(s, 1H, H_A), 4.76 and 4.72(2 x d, 2 x 1H, OCH_2), 4.59(m, 2H, NCH_2), 3.62(d, 1H, J 14.5Hz), 3.56(s, 3H, OMe) and 2.87(d, 1H, J 14.7Hz); m/z(%) 372(M^+,9), 313(85), 229(28), 170(18), 169(15), 144(59) and 143(100).

Single Crystal X-ray Analysis

All four structures were solved using direct methods (SHELX86)[20] and refined by full-matrix least-squares (SHELX76).[21] The non-hydrogen atoms of all four compounds were refined with anisotropic thermal parameters with the exception of the two carbon atoms of the terminal vinyl group in compound (15) which were refined isotropically. For compounds (9a) and (10b) all hydrogen atoms were located using Fourier difference syntheses and were refined with individual isotropic thermal parameters with the exception of the methyl hydrogen atoms of (9a) which were constrained as regular tetrahedra and were assigned to an overall isotropic thermal parameter. For compounds (15) and (16) all hydrogen atoms were included in calculated postions and were assigned to an overall isotropic thermal parameter with the exception of the hydrogens of the terminal vinyl group of compound (15) which were not included.

Drawings of compounds (9a), (10b), (15) and (16) are shown in Figures 1, 2, 3 and 4 respectively. Details of data collection and structure refinement together with relevant crystal data are given in Table 3.

We thank the Dr. O. Howarth, SERC High Field N.M.R. Service, Warwick University and Dr. Ian Whitcombe, Roche Products, Welwyn for high field n.m.r. spectra, and the SERC and Queen's and Leeds Universities for support

Table 3. Crystal data, data collections and refinement parameters for (9a), (10b), (15) and (16).

Compound	9a	10b	15	16
Crystal Data				
Formula	$C_{22}H_{21}NO_5$	$C_{20}H_{19}NO_3$	$C_{25}H_{25}N_2O_5$	$C_{25}H_{25}N_2O_5$
M	379.41	321.38	433.48	433.48
System	monoclinic	orthorhombic	orthorhombic	orthorhombic
a/A	1.6471(16)	8.293(3)	8.883(3)	10.432(3)
b/A	12.160(12)	16.945(5)	15.164(4)	10.742(3)
c/A	9.531(10)	22.495(8)	33.718(9)	19.819(5)
β/ °	101.2(1)	-	-	-
U/nm^3	1.873(3)	3.163(2)	4.542(2)	2.2209(11)
Z	4	8	8	4
D_c/g cm^{-3}	1.35	1.35	1.27	1.30
Space Group	$P2_1/a$ (= $P2_1/c$)	*Pbca*	$P\,2_12_12_1$	$P\,2_12_12_1$
F (000)	800	1360	1832	916
μ/cm^{-1}	0.57	0.52	0.53	0.54
Data collection[a]				
Machine used	Stoe STADI-2	Siemens P3/V2000	Nicolet P3/F	Nicolet P3/F
Scan width / ° + α-doublet splitting	[b]	2.0	1.8	2.0
Scan speeds / ° min^{-1}	3.0	2.0 - 29.3	2.0 - 29.3	2.0 - 29.3
Data collection range	3.0<θ<30.0°	1.5<θ<27.5°	2.0<θ<22.5°	2.0<θ<25.0°
Total data collected	2265	3645	3506	2321
Number Observed	3377	2155	2824	2018
Condition for an observed reflection	$F > 6.0\sigma(F)$	$F > 6.0\sigma(F)$	$F > 3.0\sigma(F)$	$F > 3.0\sigma(F)$
Structure refinement				
No. of parameters	320	293	512	272
weighting factor *g*[c]	0.00051	0.00395	0.0	0.0004
R	0.057	0.046	0.092	0.046
R_w	0.064	0.056	0.074	0.046

FOOTNOTES

a Molybdenum-Kα radiation (λ = 0.71069 A) was used in all four cases

b For (9a) a fixed scan width of 1.5° was used

c Weighting scheme used in all cases is $w^{-1} = [\sigma^2(F_0) + g(F_0)^2]$

References

1. Part 26. Grigg, R,; Henderson, D., and Sridharan, V., *Tetrahedron*, in press.
2. Grigg, R.; *Chem. Soc. Rev.*, 1987, 16, 89-121.
3. Grigg, R.; Kemp, J., Sheldrick, G., and Trotter, J., *J. Chem. Soc., Chem. Commun.*, 1978, 109-111; Joucla, M.; Hamelin, J., *Tetrahedron Letters*, 1978, 2885-2888.
4. Grigg, R.; Surendrakumar, S., Thianpatanagul, S., and Vipond, D., *J. Chem. Soc, Perkin Trans. 1*, 1988, 2693-2701; Grigg., Idle, J., McMeekin, P., Surendrakumar, S., and Vipond, D., *ibid*, 1988, 2703-2713; Rizzi, G.P.; *J. Org. Chem.*, 1971, 36, 1710-1711.
5. Tsuge, O.; Kanemasa, S., Ohe, M., and Iakenaka, S., *Bull. Chem. Soc. Jpn.*, 1987, 60, 4079-4089.
6. Grigg, R.; Thianpatanagul, S., and Kemp, J., *Tetrahedron*, 1988, 44, 7283-7292.
7. Aly, M.F.; Grigg, R., Thianpatanagul, S., and Sridharan, V., *J. Chem. Soc., Perkin Trans. 1*, 1988, 949-955.
8. Grigg, R.; Henderson, D., and Hudson, A.J. *Tetrahedron Letters*, 1989, 30, 2841-2844.
9. 1,3-Dipolar Cycloaddition Chemistry, *Ed A. Padwa, Wiley-Interscience*, Vol. 1 and 2, 1984.
10. Grigg, R., Jordan, M., and Malone, J.F., *Tetrahedron Letters*, 1979, 3877-3878; Armstrong, P.; Grigg, R., Jordan, M.W., and Malone, J.F., *Tetrahedron*, 1985, 41, 3547-3558.
11. Armstrong, P.; Grigg, R., *Tetrahedron*, 1989, 45, 7581-7586.
12. Ardill, H.; Grigg, R., Sridharan, V., and Surendrakumar, S., *Tetrahedron*, 1988, 44, 4953-4966.
13. Confalone, P.N.; Huie, E.M., *J. Org. Chem.*, 1983, 48, 2994-2997; *idem*, *J. Am. Chem. Soc.*, 1984, 106, 7175-7178.
14. We concur with Confalone's observation[12] that better yields are obtained if the free base α-amino ester is preformed from the hydrochloride salt rather than generated *in situ* by addition of tertiary amine.
15. Grigg, R.; Kemp, J., and Warnock, W.J., *J. Chem. Soc., Perkin Trans. 1*, 1987, 2275-2284; Amornraska, K., Grigg, R., Gunaratne, H.Q.N., Kemp, J., and Sridharan, V., *ibid*, 1987, 2285-2296.
16. Grigg, R.; Gunaratne, H.Q.N., and Kemp, J., *J. Chem. Soc., Perkin Trans. 1*, 1984, 41-46.
17. Barr, D.A.; Grigg, R., Gunaratne, H.Q.N., Kemp, J., McMeekin, P., and Sridharan, V., *Tetrahedron*, 1988, 44, 557-570.
18. Aly, M.F.; Ardill, H., Grigg, R., Leon-Ling, S., Surendrakumar, S., and Rajviroongit, S., *Tetrahedron Letters*, 1987, 28, 6077-6080.
19. Joucla, M., Mortier, J., and Hamelin, J., *Tetrahedron Letters*, 1985, 26, 2775-2778.
20. G.M. Sheldrick, SHELXS-86, Program for Crystal Structure Solution, University of Gottingen, 1988.
21. G.M. Sheldrick, SHELX-76, Program System for X-ray Structure Determination, University of Cambridge, 1976.