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X=Y-ZH COMPOUNDS AS POTENTIAL 1,3-DIPOLES. PART 29.[1,2]

THE IMINIUM ION ROUTE TO AZOMETHINE YLIDES.

REACTION OF CYCLIC SECONDARY AMINES WITH MONO- AND BI- FUNCTIONAL ALDEHYDES

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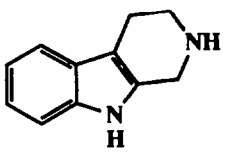
Abstract 1,2,3,4-Tetrahydro-isoquinoline and -β-carboline react with a range of mono- and bi- functional aldehydes to give azomethine ylides. The anti-dipole is formed stereospecifically or, in the case of benzaldehyde and 2-methylbenzaldehyde, stereoselectively. The effect of the structure of the aldehyde on the stereochemistry of the derived azomethine ylide is rationalised in terms of steric and electronic effects. Inter- and intra-molecular trapping of the azomethine ylides gives cycloadducts in good yield.

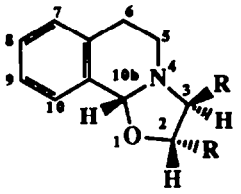
The preceding paper[1] summarised the background to the development of the iminium ion route to azomethine ylides and illustrated its' application to reactions involving primary or secondary amines and bifunctional ketones. This paper is concerned with analogous reactions involving the bifunctional aldehydes: pyridine-2-carboxaldehyde, phenyl glyoxal and ethyl glyoxalate, and with benzaldehyde and its 2-substituted derivatives. The latter aldehydes have provided important mechanistic insights.

a. Pyridine-2-carboxaldehyde. The regiospecific azomethine ylide formation involving the benzylic methylene group encountered in the reaction of 1,2,3,4-tetrahydroisoquinoline and acenaphthenequinone[1] is a general phenomenon. Thus both 1,2,3,4-tetrahydroisoquinoline and tetrahydro-β-carboline (1) react regio- and stereo-specifically with two mol. of pyridine-2-carboxaldehyde (MeCN, 80°C, 2h) to give (2)(70%) and (3)(64%) respectively. These products, whose structures were established by n.O.e. studies, are derived from *endo*-addition of the dipolarophile to the respective *anti*-dipoles (4a, partial structure).

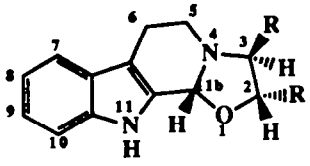
We have previously reported the conversion of (2) to a mixture of endo-(5a)- and exo-(6a)-cycloadducts on heating in acetonitrile in the presence of N-methylmaleimide.[3] This reaction proceeds via stereospecific cycloreversion of (2) to (4a). Thus, as expected, (1) reacts (MeCN, 80°C) with N-methylmaleimide (1 mol) and pyridine-2-carboxaldehyde (2 mol) to give a 2:1 mixture (63%) of *endo*-(7)- and *exo*-(8)- isomers together with the corresponding Michael adduct (9)(12%). However, in this case it is unlikely that any (3) is formed due to the high reactivity of N-methylmaleimide as a dipolarophile. The cycloadducts (7) and (8) have been prepared previously by our decarboxylative route



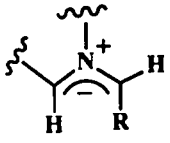
(1)



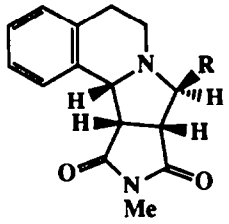
(2) R=2-pyridyl



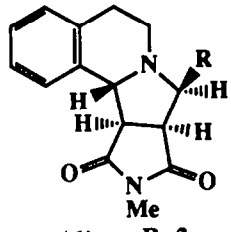
(3) R=2-pyridyl



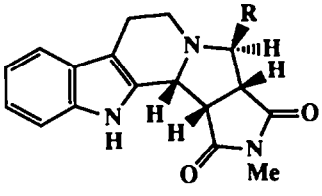
(4) a. R=2-pyridyl
b. R=COPh
c. R=CO_2Et
d. R=C_6H_5
e. R=2-MeC_6H_4



(5) a. R=2-pyridyl
b. R=Ph



(6) a. R=2-pyridyl
b. R=Ph



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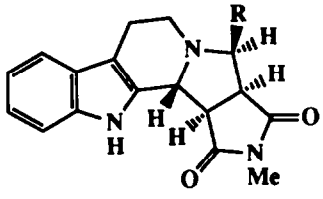
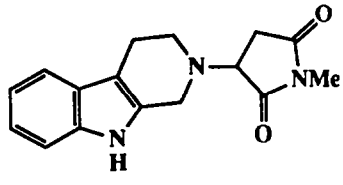


(8) R=2-pyridyl

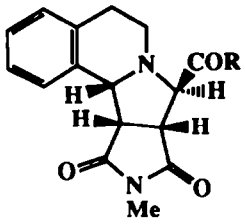


(9)

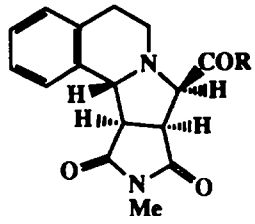
to dipoles.[3]

b. Phenylglyoxal and Ethyl Glyoxalate. 1,2,3,4-Tetrahydroisoquinoline reacts (MeCN, 80°C) with phenylglyoxal and N-methylmaleimide to give a 7:1 mixture (75%) of *endo*-(10a)- and *exo*-(11a)-cycloadducts together with Michael adduct (12) (20%). The analogous reaction with ethyl glyoxalate replacing phenylglyoxal afforded a 2:1 mixture of (10b) and (11b) in 72% yield. All these cycloadducts are derived from the respective anti-dipoles (4b) and (4c). In contrast to the mixture of endo- and exo-cycloadducts obtained from 1,2,3,4-tetrahydroisoquinoline and ethyl glyoxalate, the β-carboline (1) reacts under analogous conditions to give a single cycloadduct (13) (60%) together with Michael adduct (9) (10%).

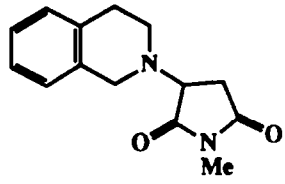
c. Benzaldehyde and 2-Substituted Benzaldehydes. Although the stereochemistry of the cycloadducts obtained from primary and secondary amines and carbonyl compounds containing the O=C–C=X moiety accords with a 1,5-H shift mechanism,[1] alternative mechanistic interpretations are possible. Studies utilising benzaldehyde and 2-substituted benzaldehydes as carbonyl components



(10) a. R=Ph
b. R=OEt



(11) a. R=Ph
b. R=OEt



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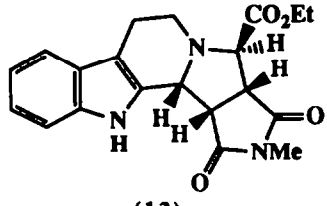
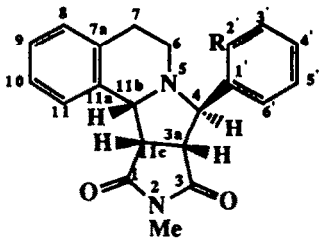


(13)

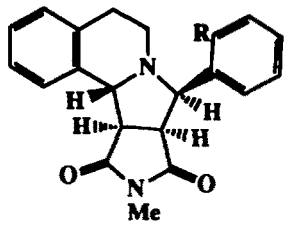
demonstrated that iminium ion formation causes a sufficient lowering of the pK_a of adjacent benzylic protons [C=N(R)C$\underline{H}_2$Ar] to promote deprotonation and consequent azomethine ylide formation. However, in these cases azomethine ylide formation is sometimes stereoselective rather than stereospecific

When 1,2,3,4-tetrahydroisoquinoline, benzaldehyde, and N-methylmaleimide are reacted in boiling toluene the product consists of a mixture (50%) of the four stereoisomeric cycloadducts (14a), (15a), (16a) and (17a) together with Michael adduct (12)(25%). It was not possible to determine the cycloadduct isomer ratio from the p.m.r. spectrum of the crude reaction mixture due to overlapping signals. However, flash chromatography and subsequent fractional crystallisation enabled pure samples of each isomer to be obtained and characterised. The flash chromatography results suggested the initial ratio of adducts derived from *anti*- (4d)- and *syn*-(18a)- dipoles was ca. 3.2:1. A similar result was obtained when benzaldehyde was replaced by 2-methylbenzaldehyde. Again a mixture of four stereoisomeric cycloadducts, (14b), (15b), (16b) and (17b), was obtained and again signal overlap in the p.m.r. spectrum of the crude product prevented determination of the ratio of the cycloadducts although it was clear that adducts derived from the *anti-dipole* (4e) predominated.

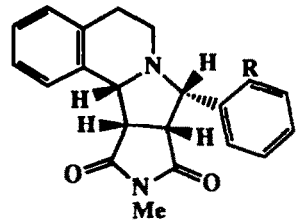
Stereochemical Assignments Detailed p.m.r. studies were carried out on one pair of endo- and exo-cycloadducts, (14c) and (15d) respectively, of an anti-dipole and on the exo-cycloadduct (15e) of another anti-dipole. These were necessary to assign unequivocally the 4-H and 11b-H benzylic proton resonances and to establish the stereochemistry. This assignment of 4-H and 11b-H resonances was based on n.O.e. enhancements between these resonances and those of 6′-H (typically 2%) and 11-H (typically 5%), respectively. In the case of (14c), irradiation of 11b-H leads to enhancements of both 6′-H (10%) and 11-H(6%). Assignment of the aromatic region of the p.m.r. spectra of these



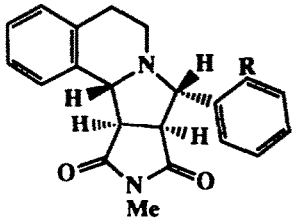
(14) a. R=H
b. R=Me
c. R=MeO
d. R=$OCH_2CH=CH_2$
e. R=$OCH_2C\equiv CH$



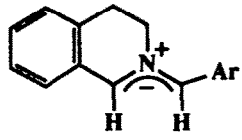
(15) a. R=H
b. R=Me
c. R=CHO
d. R=MeO
e. R=$OCH_2CH=CH_2$
f. R=$OCH_2C\equiv CH$



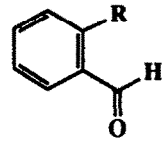
(16) a. R=H
b. R=Me



(17) a. R=H
b. R=Me



(18) a. Ar=C_6H_5



(19) a. R= CHO
b. R= OMe
c. R= $OCH_2CH=CH_2$
d. R= $OCH_2C\equiv CH$
e. R= E-$OCH_2CH=CHCO_2Me$

adducts was a pre-requisite and is described below for (15e) [note that n′-H and n′ - C refer to the protons and carbon atoms of the 4-Ar substituent in (14) and (15)]. The aromatic region of the p.m.r. spectrum consisted of eight multiplets (four apparent doublets and four apparent triplets) arising from the 8-, 9-, 10-, 11- and Ar′-H resonances. The 3′-H proton resonance was identified from its relatively high field chemical shift expected from substituent effects and its n.O.e. to/from CH_2=CH-CH_2-O (13 and 9% respectively). Partial overlap caused ambiguity in the results of an ordinary COSY spectrum. However, the assignment of 6′-H was obtained unambiguously from a COSY experiment with 2-step relayed coherence transfer.[4] In this experiment, correlations are expected between all the spins of a linear AMQX spin system. Similarly, the resonance due to 8-H was identified from its n.O.e. to/from the 7-H protons (3 and 8% respectively) and the assignment of 9, 10- and 11-H thence followed from the COSY spectra. In the case of (15e) only, confirmation of the proton assignments was provided by a ^{13}C-^{1}H COLOC (Correlation via LOng range Couplings)[5] experiment (optimised for $^{n}J(CH) \approx$ (6Hz). In this experiment, correlations were clearly observed, for example, between 4-H and 1′-C and also between 11b-H and 7a- and 11a-C. Each pair of *anti-endo* (i.e. anti dipole-endo cycloadduct) and *anti-exo* isomers give rise to a characteristic p.m.r. pattern. A typical example, a mixture of (14c) and (15d), is shown in the figure. The outer singlet and doublet arise from the 4-H and 11b-H respectively of the

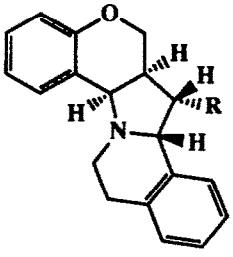
anti-endo isomer (14c) whilst the inner singlet arises from the 11b-H and inner doublet from the 4-H of the *anti-exo* isomer (15d). The chemical shifts and coupling constants of the 4-H and 11b-H of the *anti-endo* (14a-e), *anti-exo* (15a-e), *syn-endo* (16a,b) and *syn-exo* (17a,b) isomers are collected in the Table. Cycloadducts derived from the *anti*-dipole give rise to signals for the 4-H and 11b-H between δ4.3-5.2, whilst the corresponding *syn*-dipole cycloadduct signals for 4-H and 11b-H occur between δ 3.6-4.0 (Table).

Table Chemical shifts and coupling constants of cycloadducts (14)-(17).

Cycloadduct	4-H(δ)	J(Hz)	11b-H(δ)	J(Hz)
14a	4.98	0.0	4.37	9.0
14b	5.00	0.0	4.50	8.9
14c	5.18	0.9	4.53	7.7
14d	5.17	0.0	4.53	7.8
14e	5.12	0.0	4.53	7.7
15a	4.45	8.0	4.76	0.0
15b	4.79	8.2	4.95	0.0
15d	4.77	8.0	5.02	0.0
15e	4.84	8.0	5.04	0.0
15f	4.77	8.3	5.02	0.0
16a	3.80	9.0	3.91	6.0
16b	3.98	9.0	3.93	6.0
17a	3.75	7.0	3.80	8.0
17b	3.55	8.5	3.87	7.4

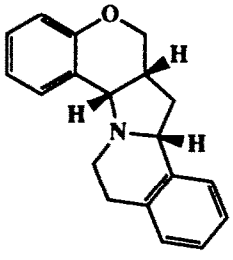
In contrast to the *anti-syn* dipole mixtures produced from 1,2,3,4-tetrahydroisoquinoline and benzaldehyde or 2-methylbenzaldehyde, the aldehydes (19a-d) react with 1,2,3,4-tetrahydroisoquinoline and N-methylmaleimide to give adducts derived solely from the corresponding *anti*-dipoles (4). Thus (19a) gives a single cycloadduct (15c) (57%) together with Michael adduct (12) (26%), whilst (19b-d) give 2:1 mixtures of *endo*- and *exo*- cycloadducts (14c) and (15d), (14d) and (15e), and (14e) and (15f) respectively. Adducts derived from the *syn*-dipole (18) were not detected. Extensive experience with maleimide dipolarophiles has shown that, due to their reactivity, they trap the dipole(s) produced under kinetic control and do not permit dipole equilibration.[6-8] It was of interest therefore to study the intramolecular cycloaddition of azomethine ylides produced from the reaction of 1,2,3,4-tetrahydroisoquinoline or the β-carboline(1) with (19c). The former reaction (xylene, 140°C, 4h) gives a 3.9:1 mixture (60%) of (20a) and (21) whilst (1) and (19c) react (xylene, 140°C, 24h) to give a 14.5:1 mixture (78%) of (22a) and (23). In cases such as these the cycloaddition step, as opposed to dipole formation, is rate determining. Moreover, there is evidence to suggest that for 1,3-diaryl azomethine

ylides, cycloaddition is slower than *syn-anti* dipole equilibration.[7,8] Thus the product ratio (20a):(21) and (22a):(23) reflects the energies of the cycloaddition transition states. This is illustrated by the reaction (xylene, 140°C) of 1,2,3,4-tetrahydroisoquinoline with (19d) to give a single cycloadduct, (24) (65%), derived from the *anti*-dipole. In this case the stereospecificity results from a kinetically controlled selection of the *anti*-dipole from an equilibrating *syn-anti* dipole mixture due to a stereochemically more favourable alignment of the four reacting centres in the cycloaddition transition state involving the *anti*-dipoles.[6] Both 1,2,3,4-tetrahydroisoquinoline and the β-carboline (1) react with aldehyde (19e)(xylene, 140°C) to give a single cycloadduct (20b) (60%) and (22b) (57%) respectively. The high dipolarophilic reactivity of an intramolecular ω- acrylate moiety has been noted before and it has been shown to trap



(20) a. R=H

b. R=CO_2Me



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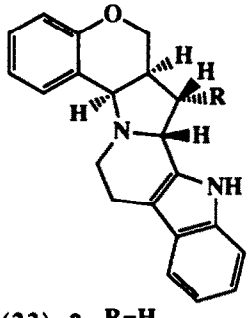
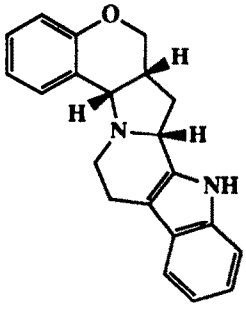


(22) a. R=H

b. R=CO_2Me



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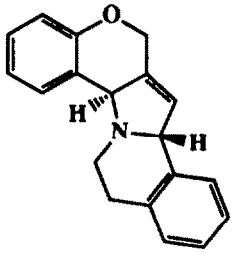
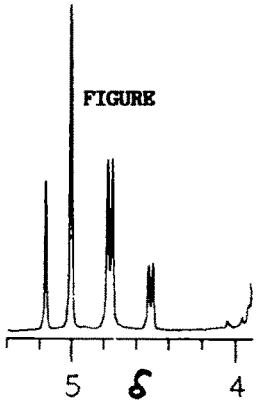


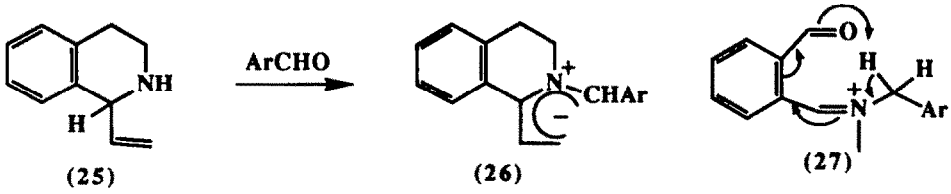
(24)



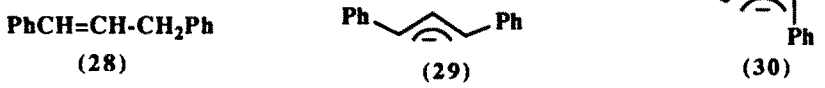
the dipole(s) formed under kinetic control and not to permit dipole equilibration.[6] The intramolecular cycloaddition products (20)-(24) have been prepared previously via the decarboxylative route to azomethine ylides.[7]

Mechanism. It is clear from the foregoing results that iminium ions with adjacent benzylic protons [C=N(R) $C\underline{H}_2Ar$] undergo facile deprotonation to generate azomethine ylides and we have previously shown that analogous deprotonation occurs in certain doubly activated α-vinyl secondary amines e.g. (25) → (26).[9] The 1,5-H shift route to azomethine ylides envisaged at the outset of this work[1,2]

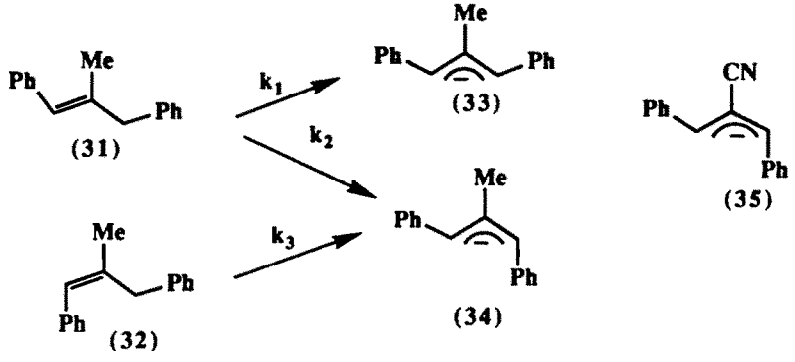
correctly predicts the observed azomethine ylide stereochemistry when bifunctional carbonyl compounds O=C-C=X are used to generate the azomethine ylides. However, analogous stereospecific anti-dipole formation is observed with the 2-substituted benzaldehydes (19a-e) which are not able to participate in a 1,5-H shift mechanism. Aldehyde (19a) could participate in azomethine ylide formation via a 1,7-H shift but only at the expense of destroying the aromaticity of the benzene ring i.e. (27, arrows). Thus alternative stereoelectronic influences need to be invoked for (19a-e) which could negate the operation of a 1,5-H shift mechanism in the case of bifunctional carbonyl compounds.



(25) (26) (27)



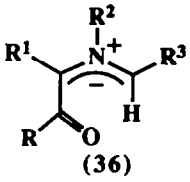
(28) (29) (30)



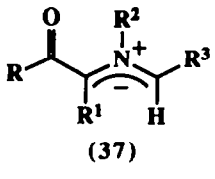
(31) (33) (35) (32) (34)

It seems reasonable to expect that the influence of steric and electronic factors on the configuration of allyl anions and azomethine ylides will be broadly similar. A possible complicating factor is the effect of the gegenion in the case of the allyl anions. However, there is good evidence that the alkali metal salts of allyl anions exist as solvent separated ion pairs in polar solvents[10] and that the gegenions do not markedly influence either the configurational preferences or ratios[11] unlike the pentadienyl anion case.[12] It has been established that deprotonation (THF, -30°C) of (28) gives a ca. 94:6 mixture of *syn*-(29)- and *anti*-(30)-allyl anions[13] [$\Delta\Delta G_{0(17°C)}$ 1.2 kcal/mol] and the formation of (29) is substantially faster than formation of (30).[14] In contrast deprotonation of both (31) and (32) results in formation of (34)[15] due to steric destabilisation of (33) arising from the contiguous Ph/Me/Ph interactions and

additionally $k_3 > k_2 >> k_1$.[16] Similarly the *anti*-isomer (35) of the sterically less demanding 2-cyano anion is more stable than its *syn*-isomer.[10] Thus in all cases involving azomethine ylide formation from aldehydes and secondary amines we would expect the *anti*-dipole to form at a faster rate and to be thermodynamically more stable than the *syn*-dipole. Two observations remain to be explained: (i) the progression from stereoselective to stereospecific formation of the *anti*-azomethine ylide as the aldehyde component is varied from benzaldehyde or 2-methylbenzaldehyde to the 2-substituted aryl aldehydes (19a-e) and (ii) factors favouring the formation of azomethine ylide (36) rather than (37) - (39) from reactions involving amines and bifunctional aldehydes if a 1,5-H shift mechanism is not operating. Note that azomethine ylide (39) cannot form in cases where cyclic secondary amines are used since R^2/R^3 are linked in a 5- or 6-membered ring.



(36)



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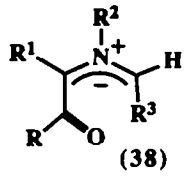

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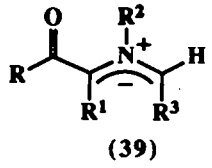

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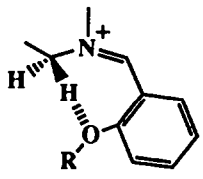

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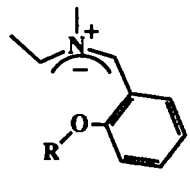

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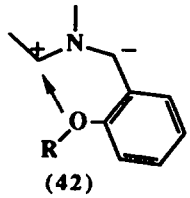

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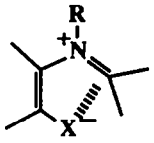
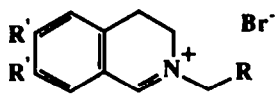
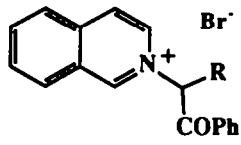


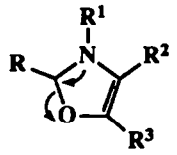
(43)



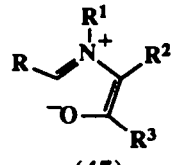
(44) R=CO_2Me, COPh, p-$O_2NC_6H_4$



(45)



(46)



(47)

The difference between the stereoselective *anti*-dipole formation observed when 2-methylbenzaldehyde is the aldehyde component and stereospecific *anti*-dipole formation with (19a-e) seems unlikely to be wholly steric in origin. Whatever the nature of the effect it need only furnish a

1-2 kcal advantage to the *anti*-dipole since this is already favoured over the *syn*-dipole by a factor of ca. 3:1. The effect may arise from initial hydrogen bonding of the oxygen to the acidic benzylic protons in the intermediate iminium ion (40) which transmutes into stabilisation of the developing dipole by lone pair interaction, of the type shown in canonical form (42), as deprotonation, by an external base, to (41) proceeds. Alternatively (42) can be regarded as the interaction of a filled oxygen lone pair orbital with the LUMO of the developing dipole. Similar effects are possible with (19a) and with the bifunctional ketones (e.g. 43)[2] discussed in the preceding paper. The benzaldehyde and 2-substituted benzaldehyde cycloadditions were all carried out in a non-polar solvent (toluene) which should encourage such interactions. Thus it is not necessary to invoke a concerted sigmatropic 1,5-H shift in the iminium ion route to azomethine ylides. The observed stereospecificity arises from a combination of steric and electronic interactions as discussed above.

There have been several reports of the generation and trapping azomethine ylides by deprotonation of preformed iminium salts (44)[17] and (45).[18,19] Where the stereochemistry of the cycloadducts was established it accords with anti-dipole formation. Tsuge[19] proposed a similar charge interaction to (43) as responsible for *anti*-dipole formation but did not appreciate the major role of steric factors. The recent work of Vedejs[20] involving 4-oxazolines as azomethine ylide precursors (46) = (47) is also relevant. Interestingly if R^3 = alkyl or aryl, the oxazoline (46) resists ring opening, probably due to steric interactions in the dipole (47).

Experimental Experimental details are as previously noted.[21] Petroleum ether refers to the fraction with b.p. 40-60°C. Flash chromatography employed Silica Gel 60 (Merck).

Pyridine-2-carboxaldehyde Cycloadducts

2α,3β,6,10b-Tetrahydro-2,3-di-(2′-pyridyl)-5H-oxazolo[2,3-a]isoquinoline (2). A solution of 1,2,3,4-tetrahydroisoquinoline (670mg, 5 mmol) and pyridine-2-carboxaldehyde (1.07g, 10 mmol) in acetonitrile (50 ml) was boiled under reflux for 2 h. The solvent was removed under reduced pressure to give the *product* as an off-white solid (1.16g, 70%) which crystallised from ether-petroleum ether as colourless rods m.p. 133-134°C. (Found: C, 76.6; H, 5.85; N, 12.75. $C_{21}H_{19}N_3O$ requires C, 76.55; H, 5.8; N, 12.75%); ν_{max} 1585, 1560, 1430, 770, 760 and 720 cm^{-1}; m/z(%) 329 (M^+, 17), 251(3), 222(11), 130(72) and 93(100); δ 2.74-2.80(m, 1H, 6-H), 2.99-3.26(m, 3H, 5- and 6-H), 4.71 (d, 1H, 3-H, J 4.69Hz), 5.53(d, 1H, 2-H, J4.70Hz), 5.78(s, 1H, 10b-H), 7.12-7.74(m, 10H, ArH), 8.59(m, 1H, pyα-H) and 8.67(m, 1H, pyα-H); ^{1}H NOEDSY (%): irradiation of 2-H caused enhancements of 3-H(5) and ArH(3); irradiation of 10b-H caused enhancement of ArH(15); stereochemistry was also assigned by comparison with (3).

2α,3β,5,6-Tetrahydro-2,3-di-(2′-pyridyl)-oxazolo[3′,2′-1,2]pyrido[3,4-b]indole (3). A solution of 1,2,3,4-tetrahydro-β-carboline(860 mg, 5 mmol and pyridine-2-carboxaldehyde (1.07g, 10 mmol) in acetonitrile (50 ml) was boiled under reflux for 2 h. T.l.c., eluting with 4:1 v/v Et_20-ethyl acetate, showed one spot with R_f 0.43. Purification by flash chromatography gave the *product* (1.18g, 64%) which crystallised from ether-petroleum ether as colourless rods, m.p. 163-164°C (Found: C, 75.45; H, 5.35; N, 15.2. $C_{23}H_{20}N_4O$ requires C, 74.95; H, 5.45; N, 15.2%); ν_{max} 3345, 1587, 1432, 1171, 1029 and

735 cm^{-1}; m/z(%) 368(M^+, 4), 261(12), 183(17), 171(20) and 107(28); δ2.81-2.86(m, 2H, 6-H), 3.10-3.21(m, 2H, 5-H), 4.64(d, 1H, 3-H, J 5.27Hz), 5.57(d, 1H, 2-H, J 5.29Hz), 5.96(s, 1H, 11b-H), 7.03-7.67(m, 10H, ArH), 8.61(d, 1H, pyα-H), 8.63(d, 1H, pyα-H) and 9.00(s, 1H, NH); ^{1}H NOEDSY (%): irradiation of 2-H caused enhancements of 3-H (2) and 11b-H(3); irradiation of 3-H caused enhancements of 2-H(4) and 5-H(6); irradiation of 11b-H caused enhancements of 2-H(3) and NH(3).

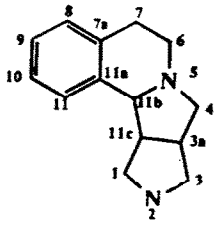
1,2,3,3aα,4β,6,7,12,12bα,12cα-Decahydro-2-methyl-4-(2′-pyridyl)-pyrrolo[3′,4′-1,2]indolizino[8,7-b]indole-1,3-dione(7) and 1,2,3,3aα,4α,6,7,12,12bβ,12cα-decahydro-2-methyl-4-(2′-pyridyl)-pyrrolo[3′,4′-1,2]indolizino[8,7-b]indole-1,3-dione(8). A solution of 1,2,3,4-tetrahydro-β-carboline (1.0g, 5.8 mmol), pyridine-2-carboxaldehyde (1.24g, 11.6 mmol) and N-methylmaleimide (650 mg, 5.8 mmol) in acetonitrile (30 ml) was boiled under reflux for 2 h. The solvent was then removed under reduced pressure, the residue dissolved in chloroform and washed with water. The dried (anhy. Mg SO_4) chloroform solution was evaporated to dryness and the residue triturated with ether-petroleum ether to afford a yellow solid (2.02g, 93.5%) whose p.m.r. spectrum showed it to comprise a 2:1 mixture of cycloadducts (7) and (8) together with some Michael adduct (9). Preparative t.l.c. (silica) eluting with 19:1 v/v chloroform-methanol afforded (7) (980mg, 45%), m.p. and (8)(490mg, 23%), together with Michael adduct (9), (260mg, 12%), m.p. 252-254°C.

(7) Colourless plates (ethanol) m.p. 283-284°C. (Found: C, 70.85; H, 5.45; N, 15.05%); ν_{max} 3400, 1760, 1690, 780 and 755 cm^{-1}; m/z(%) 372(M^+, 71), 371(11), 280(100), 261(12) and 171(21); δ($CDCl_3$, CF_3COOD); 2.91(m, 2H, 7-H), 2.98(s, 3H, NMe), 3.29(m, 1H, 6-H), 3.61(m, 1H, 6-H), 4.12(m, 2H, 3a-H and 12c-H), 5.44(m, 1H, 4-H), 5.64(s, 1H, 12b-H) and 7.12-8.84(m, 8H, ArH); ^{1}H NOEDSY(%): irradiation of 4-H caused enhancements of 3a-H(13) and py-H(6); irradiation of 12b-H caused enhancements of 12c-H(3) and 6-H(3). The signals for 3a-H and 12c-H were too close together to irradiate separately.

(8) Colourless prisms (methanol) m.p. 206-207°C (Found: C, 71.1; H, 5.55; N, 14.8. $C_{22}H_{20}N_4O_2$ requires C, 70.95; H, 5.4; N, 15.05%); ν_{max} 3400, 1765, 1690, 785, 760 and 745 cm^{-1}; m/z(%) 372(M^+,68), 371(9), 280(100), 261(15), 169(21); δ 2.58-3.86(m, 4H, 2 x 6- and 2 x 7-H), 2.84(s, 3H, NMe), 3.88(dd, 1H, 3a-H, J 4.8 and 8.9Hz), 4.02(t, 1H, 12c-H, J 8.8Hz), 4.53(d, 1H, 4-H, J 4.8Hz), 5.02(d, 1H, 12b-H, J 8.6Hz), 7.04-7.47(m, 6H, ArH), 7.72(dt, 1H, py γ-H), 8.56(s, 1H, NH) and 8.68(dd, 1H, pyα-H); ^{1}H NOEDSY (%): irradiation of 3a-H caused enhancements of 12c-H (6) and 4-H(3); irradiation of 4-H caused enhancements of 3a-H (3) and py γ-H (10); irradiation of 12b-H caused enhancements of NH (3) and 12c-H(13); irradiation of 12c-H caused enhancements of 12b-H(13) and 3a-H(5).

(9) Identical to that described below.

Phenyl Glyoxal and Ethyl Glyoxalate Cycloadducts



2,3,3a,4,6,7,11b, 11c-Octahydro-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline skeleton.

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4-benzoyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(10a) and 2,3,3aα,4α,6,7,11bβ,11cα-octahydro-2-methyl-4-benzoyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione (11a). A solution of 1,2,3,4-tetrahydroisoquinoline (670 mg, 5 mmol), phenyl glyoxaldehyde (670 mg, 5 mmol), and N-methylmaleimide (560 mg, 5 mmol) in acetonitrile (50 ml) was boiled under reflux for 2 h. T.l.c., eluting with 7:3 v/v ether-chloroform, showed three spots, R_f 0.54, 0.46, 0.23. The two isomeric cycloadducts and the Michael adduct were separated by preparative t.l.c. to give (10a) (1.19g, 66%), (11a) (160 mg, 9%) and (12) (360 mg, 20%).

(10a) Colourless prisms (methanol) m.p. 176-178°C (Found: C, 73.25; H, 5.45; N, 7.8. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.75%); ν_{max} 3400, 1770, 1690, 1450 and 755 cm^{-1}; m/z(%) 360 (M^+,12), 331(11), 256(18), 255(100) and 170(13); δ 2.83(m, 3H, 6-H and 7-H), 2.88(s, 3H, NMe), 3.16(m, 1H, 6-H), 3.75(t, 1H, 11c-H, J 7.9Hz), 3.84(dd, 1H, 3a-H, J 0.7, 8.0Hz), 4.70(d, 1H, 11b-H, J 7.8Hz), 5.16(d, 1H, 4-H, J 0.9Hz) and 7.07-8.15(m, 9H, ArH); ^{1}H NOESDY (%): irradiation of 11b-H caused enhancements of 11c-H (16), 3a-H (2) and ArH (9); irradiation of 11c-H caused enhancements of 11b-H (20) and 3a-H (10); irradiation of 3a-H caused enhancements of 11c-H (9) and 4-H (5); irradiation of 4-H caused enhancements of 3a-H (7) and ArH (30).

(11a) Colourless needles (methanol) m.p. 156-158°C (Found: C, 73.0; H, 5.75; N, 7.55. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.75%); ν_{max} 3560, 1770, 1690, 1450 and 765 cm^{-1}; m/z(%) 360 (M^+, 2), 359(1), 256(23), 255(100) and 170(12); δ 2.58(m, 4H, 6-H and 7-H), 3.03(s, 3H, NMe), 3.57(dd, 1H, 11c-H, J 3.2, 8.7Hz), 3.75(t, 1H, 3a-H, J 8.2Hz), 4.85(d, 1H, 11b-H, J 2.2Hz), 4.98(d, 1H, 4-H, J 7.8Hz) and 7.07-8.03(m, 9H, ArH); ^{1}H NOESDY (%): irradiation of 11c-H caused enhancements of 11b-H (5) and 3a-H(10); irradiation of 3a-H caused enhancements of 11c-H(12) and 4-H(10); irradiation of 4-H caused enhancement of 3a-H(14).

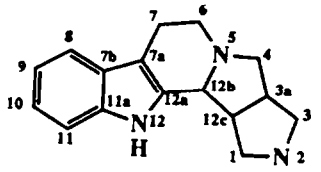
(12) Colourless rods (chloroform - petroleum ether), m.p. 134-136°C. Identical to that described previously.[1]

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4-ethoxycarbonyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(10b) and 2,3,3aα,4α,6,7,11bβ,11cα-octahydro-2-methyl-4-ethoxycarbonyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(11b). A solution of 1,2,3,4-tetrahydroisoquinoline (1.0g, 7.5 mmol), ethyl glyoxalate (900 mg, 7.5 mmol) and N-methylmaleimide (840 mg, 7.6 mmol) in acetonitrile (30 ml) was boiled under reflux for 24h. The solvent was then removed under reduced pressure, the residue dissolved in chloroform and washed with water. The dried (anhy. Na_2SO_4) chloroform extract was evaporated to give an off white solid whose p.m.r. spectrum showed it to comprise a 2:1 mixture of endo-(10b)- and exo-(11b)-isomers together with a some Michael adduct (12). The cycloadducts were separated by preparative t.l.c. (silica) eluting with 19:1 v/v chloroform - methanol.

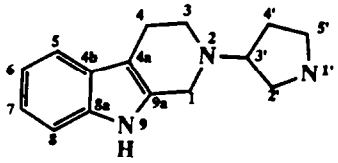
(10b) Colourless prisms (1.18 g, 48%), m.p. 121-123°C, from ether-petroleum ether (Found: C, 65.9; H, 6.15; N, 8.55. $C_{18}H_{20}N_2O_4$ requires C, 65.85; H, 6.1; N, 8.55%); ν_{max} 1780, 1720, 1690, 1430, 1380, 1180, 1120 and 760 cm^{-1}; m/z(%) 328,(M^+, 23), 299(29), 256(17), 255(100), 170(13) and 145(8); δ 1.31(t, 3H, $CH_2\underline{Me}$), 2.70(dd, 1H, 7-H, J 14.7 and 3.3Hz), 2.94(m, 2H, 6-H and 7-H), 3.15(m, 1H, 6-H), 3.61(d, 1H, 3aβ-H, J 7.7Hz), 3.71(t, 1H, 11cβ-H, J 7.5Hz), 4.22(s+m, 3H, $\underline{CH_2}Me$ and 4α-H), 4.49(d,

1H, 11bβ-H, J 7.3Hz), 7.07(d, 1H, ArH), 7.19(m, 2H, ArH) and 7.44(d, 1H, ArH).

(11b) Colourless solid (590 mg, 24%) admixed with a small amount of Michael adduct(12). δ 1.3(t, 3H, CH_2Me), 2.59(d, 1H, 7-H, J 16.5Hz), 3.03(s, 3H, NMe), 3.00, 3.12, 3.30(3 x m, 3 x 1H, 2 x 6-H, 7-H), 3.55(t, 1H, 3aα-H, J 8.2Hz), 4.02(d, 1H, 11cα-H, J 7.8Hz), 4.27(m, 3H, CH_2Me and 4α-H), 4.76(s, 1H, 11bβ-H), 7.08(d, 1H, ArH), 7.22(m, 2H, ArH) and 7.44(d, 1H, ArH).



1,2,3,3a,4,6,7,12,12b,12c-Decahydropyrrolo[3′,4′-1,2]indolizino[8,7-b]indole skeleton.



(9) skeleton

1,2,3,3aα,4β,6,7,12,12bα,12cα-Decahydro-4-ethoxycarbonyl-2-methyl-pyrrolo[3′,4′-1,2]indolizino[8,7-b]indole-1,3-dione (13). A solution of 1,2,3,4-tetrahydro-β-carboline (860 mg, 5 mmol), ethyl glyoxylate (510 mg, 5 mmol), and N-methylmaleimide (560 mg, 5 mmol) in acetonitrile (50 ml) was boiled under reflux for 15 h. The solvent was removed under reduced pressure to give the *product* as an off-white solid (1.10 g, 60%), along with Michael adduct (9) (180 mg, 10%).

(13) Crystallised from chloroform-methanol as colourless prisms, m.p. 180-181°C (Found: C, 65.35; H, 5.7; N, 11.4. $C_{20}H_{21}N_3O_4$ requires C, 65.4; H, 5.7; N, 11.45%); ν_{max} 3400, 1770, 1690, 1450 and 755 cm^{-1}; m/z(%) 367(M^+, 98), 338(68), 294(100), 256(45) and 183(14); δ(C_6D_6) 0.95(t, 3H, CH_2CH_3), 2.34(s, 3H, NMe), 2.44(m, 1H, 7β-H), 2.68(m, 1H, 6α-H), 2.73-2.82(m, 1H, 7αH), 3.04(m 1H, 6β-H), 3.09(t, 1H, 12c-H, J 8.2Hz), 3.20(dd, 1H, 3a-H, J 1.3 and 8.02Hz), 3.90(m, 2H, CH_2CH_3), 4.35(s, 1H, 4-H), 4.46(d, 1H, 12b-H, J 8.3Hz), 7.17-7.28(m, 3H, ArH), 7.49(d, 1H, ArH) and 8.17(s, 1H, NH); ^{1}H NOESDY (%): irradiation of NH caused enhancements of 12b-H (2) and 12c-H (2); irradiation of 12b-H caused enhancements of NH (2), 12c-H (9) and 6α-H (3); irradiation of 3a-H caused enhancement of 4-H (4). There was difficulty in irradiating the four signals separately due to their close chemical shift values.

2-[3′-(2′,5′-Dioxo-1′-methylpyrrolidinyl)]-1,2,3,4-tetrahydro-β-carboline (9). Colourless rods (ethanol) m.p. 253-254°C. (Found: C, 67.7; H, 5.95; N, 14.65. $C_{16}H_{17}N_3O_2$ requires C, 67.8; H, 6.05; N, 14.85%); ν_{max} 3280, 1770, 1690, 1440, 1290, 750 and 700 cm^{-1}; m/z(%) 283(M^+, 29), 172(13) and 143(100); δ 2.80-3.00(m, 6H, 1-, 3- and 4-H), 3.04 (s, 3H, NMe), 3.87(d, 1H, 4′-H, J 15Hz), 4.00(q, 1H, 3′-H, J 4.8Hz), 4.18(d, 1H, 4′-H, J 15Hz), 7.08-7.48(m, 4H, ArH) and 7.77(s, 1H, NH).

Benzaldehyde and 2-Substituted Benzaldehyde Cycloadducts

2,3,3a,4,6,7,11b,11c-Octahydro-2-methyl-4-phenyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(14a),(15a),(16a) and (17a). A solution of 1,2,3,4-tetrahydroisoquinoline (670mg, 5 mmol)

benzeldehyde (530 mg, 5 mmol), and N-methylmaleimide (560 mg, 5 mmol) in toluene (50 ml) was boiled under reflux for 1.5h. T.l.c. (silica), eluting with 4:1 v/v Et_2O-petroleum ether, showed four spots, R_f 0.62, 0.42, 0.17, 0.09(iodoplatinate spray). These components were separated by flash chromatography to give (17a) (100 mg, 6.5%), (14a) and (15a) as a mixed fraction (640 mg, 38%), Michael adduct (12) (410 mg, 25%) and (16a) (90 mg, 5.5%), giving a total isolated yield of cycloadducts of 50%. Fractional crystallisation (methanol) gave a pure sample of (15a). A second separation was carried out on the mother liquor, eluting with 1:1 v/v Et_20 - petroleum ether. Partial separation was accomplished, the early fractions containing sufficient (14a) for characterisation. The stereochemical assignment of the four cycloadducts was achieved by comparison with the products from the analogous reaction carried out using 6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline-1-carboxylic acid.[3]

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4-phenyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione (14a). Colourless prisms (methanol) m.p. 220-223°C (decomp.) (Found: C, 75.85; H, 6.05; N, 8.7%); ν_{max} 1770, 1690, 1430, 770, 745 and 700 cm^{-1}; m/z(%) 332(M^+, 82) 331(66), 222(18) and 221(100); δ($CDCl_3$/DMSO-d_6) 2.35-2.44(m, 1H, 7-H), 2.85-3.24(m, 3H, 2 x 6-H and 7-H), 2.97(s, 3H, NMe), 3.34(t, 1H, 3a-H, J 8.5Hz), 3.56(d, 1H, 11c-H, J 8Hz), 4.37(d, 1H, 4-H, J 9Hz), 4.98(s, 1H, 11b-H) and 7.08-7.40(m, 9H, ArH).

2,3,3aα,4α,6,7,11bβ,11cα-Octahydro-2-methyl-4-phenyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15a). Colourless prisms (ethanol) m.p. 113-115°C (Found: C, 75.75; H, 6.1; N, 8.6. $C_{21}H_{20}N_2O_2$ requires C, 75.9; H, 6.05; N, 8.45%); ν_{max} 1770, 1695, 760, 755, 730 and 710 cm^{-1}; m/z(%) 332 (M^+, 13) and 221(15); δ 2.24-2.43(m, 1H, 7-H), 2.63-3.01(m, 3H, 2 x 6-H and 7-H), 2.89(s, 3H, NMe), 3.62(d, 1H, 3a-H, J 8Hz), 3.81(t, 1H, 11c-H, J 8Hz), 4.45(d, 1H, 11b-H, J 8Hz), 4.76(s, 1H, 4-H) and 7.05-7.48(m, 9H, ArH).

2,3,3aα,4α,6,7,11bα,11cα-Octahydro-2-methyl-4-phenyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(16a). Colourless fine needles (methanol) m.p. 232-233°C (Found: C, 76.1; H, 6.15; N, 8.25%); ν_{max} 1770, 1700, 760, 745, 710 and 700 cm^{-1}; m/z(%) 332(M^+, 49), 331(50), 222(18), 221(100) and 117(30); δ 2.20-2.36(m, 1H, 7-H), 2.85-3.20(m, 3H, 2 x 6-H and 7-H), 2.80(s, 3H, NMe), 3.50(dd, 1H, 3a-H, J 7 and 9Hz), 3.73(t, 1H, 11c-H, J 6.5Hz), 3.80(d, 1H, 4-H, J 9Hz), 3.91(d, 1H, 11b-H, J 6Hz) and 7.12-7.56(m, 9H, ArH).

2,3,3aα,4β,6,7,11bβ,11cα-Octahydro-2-methyl-4-phenyl-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(17a). Colourless needles (methanol) m.p. 195-196°C (Found: C, 76.15; H, 6.05; N, 8.2%); ν_{max} 1770, 1690, 780, 770, 760, 750, 715 and 700 cm^{-1}; m/z(%) 332(M^+, 93), 331(91), 222(18), 221(100), 130(22) and 117(36); δ 2.35-2.46(m, 1H, 7-H), 2.74-2.83(m, 1H, 6-H), 2.95-3.20(m, 2H, 6- and 7-H), 3.07(s, 3H, NMe), 3.32(dd, 1H, 3a-H, J 7 and 8Hz), 3.48(t, 1H, 11c-H, J 8Hz), 3.75(d, 1H, 4-H, J 7Hz), 3.80(d, 1H, 11b-H, J 8Hz) and 7.10-8.0(m, 9H, ArH).

2,3,3a,4,6,7,11b,11c-Octahydro-2-methyl-4-(2′-tolyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(14b),(15b),(16b) and (17b). Prepared from 1,2,3,4-tetrahydroisoquinoline, 2-methylbenzaldehyde and N-methylmaleimide in toluene in an analogous manner to that described above but with a reaction time of 2 h. The crude product (95%) was examined by t.l.c. (silica) eluting with 7:3 v/v ether-petroleum

ether and visualising by u.v. when four spots, R_f 0.69, 0.53, 0.22 and 0.12, were apparent. Examination by p.m.r. revealed the presence of (14b) and (15b) and Michael adduct (12) but the signals for (16b) and (17b) were obscured. Separation was achieved by a combination of flash chromatography and fractional crystallisation.

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4-(2′-tolyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(14b). Colourless plates from acetone, m.p. 175-178°C (Found: C, 76.2; H, 6.3; N, 8.05. $C_{22}H_{22}N_2O_2$ requires C, 76.25; H, 6.4; N, 8.1%); δ2.3(s, 3H, Me), 2.39 and 2.85(2 x m, 2 x 1H, 2 x 7-H), 2.9(s, 3H, NMe), 2.93-3.22(m, 2H, 2 x 6-H), 3.41(t, 1H, 11c-H, J 8.4Hz), 3.55(d, 1H, 3a-H, J 7.9Hz), 4.5(d, 1H, 11b-H, J 8.9Hz), 5.0(s, 1H, 4-H) and 7.10 - 7.38(m, 8H, ArH).

2,3,3aα,4α,6,7,11bβ,11cα-Octahydro-2-methyl-4-(2′-tolyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15b). Obtained as a mixture with (14b). The p.m.r. data is extracted from the spectrum of the mixture. δ 2.41(m, 1H, 7-H), 2.55(s, 3H, Me), 2.87(m, 1H, 7-H), 2.85(s, 3H, NMe), 3.0-3.22(m, 2H, 2 x 6-H), 3.45(d, 1H, 11c-H, J 7.6 Hz), 3.78(t, 1H, 3a-H, J 8.1Hz), 4.79(d, 1H, 4-H, J 8.2Hz), 4.95(s, 1H, 11b-H) and 7.03-7.25(m, 8H, ArH).

2,3,3aα,4α,6,7,11bα,11cα-Octahydro-2-methyl-4(2′-tolyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(16b). Colourless needles from ethanol, m.p. 178-181°C δ2.3(m, 1H, 7-H), 2.46(s, 3H, Me), 2.72(s, 3H, NMe), 2.76(m, 1H, 7-H), 3.11-3.22(m, 2H, 2 x 6-H), 3.58(dd, 1H, 11c-H, J 7.5 and 9.0Hz), 3.76(dd, 1H, 3a-H, J 7.5 and 6.0Hz), 3.93(d, 1H, 11b-H, J 6.0Hz), 3.98(d, 1H, 4-H, J 9.0Hz) and 7.13-7.55(m, 8H, ArH).

2,3,3aα,4β,6,7,11bβ,11cα-Octahydro-2-methyl-4-(2′-tolyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(17b). Colourless needles from ethanol, m.p. 200-203°C (Found: C, 76.25; H, 6.45; N, 8.25%) δ 2.34(m, 1H, 7-H), 2.43(s, 3H, Me), 2.67-2.99(m, 3H, 2 x 6-H and 7-H), 3.03(s, 3H, NMe), 3.33(t, 1H, 3a-H, J 8.1Hz), 3.49(t, 1H, 11c-H, J 8.8Hz), 3.55(d, 1H, 4-H, J 8.5Hz), 3.87(d, 1H, 11b-H, J 7.4Hz), and 7.08-7.98(m, 8H, ArH).

2,3,3aα,4α,6,7,11bβ,11cα-Octahydro-2-methyl-4-(2′-formylphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15c). A solution of 1,2,3,4-tetrahydroisoquinoline (670 mg, 5 mmol), o-phthalaldehyde (670 mg, 5 mmol) and N-methylmaleimide (560 mg, 5 mmol) in toluene (50 ml) was boiled under reflux for 2.5h. Work-up in the usual way followed by flash chromatography gave (15c) (1.02g, 57%) and Michael adduct (12) (470 mg, 26%).

(15c) Obtained as colourless plates, m.p. 192-193°C, from ethanol (Found: C, 73.15; H, 5.6; N, 7.8. $C_{22}H_{20}N_2O_3$ requires C, 73.3; H, 5.6; N, 7.75%); ν_{max} 2910, 1760, 1700, 1570, 1430 and 770cm^{-1}; m/z(%) 360(M^+, 33), 359(11), 331(11), 249(9), 134(60) and 132(100); δ 2.34(m, 1H, 7-H), 2.87(s, 3H, NMe), 3.01(m, 3H, 2 x 6-H and 7-H), 3.57(d, 1H, 11c-H, J 8.09Hz), 3.79(t, 1H, 3a-H, J 8.38Hz), 5.04(s, 1H, 11b-H), 5.31(d, 1H, 4-H, J 8.89Hz), 7.05-7.87(m, 8H, ArH) and 10.11(s, 1H, CHO); [1] NOEDSY (%): irradiation of 4-H caused enhancements of 3a-H(19), CHO(5) and ArH(2); irradiation of 3a-H caused enhancements of 4-H(13) and 11c-H(11); irradiation of 11c-H caused enhancements of 11b-H(6), 3a-H(13) and ArH(19); irradiation of 11b-H caused enhancements of 11c-H(5) and ArH(3); irradiation of CHO caused enhancements of 4-H(4) and ArH(27).

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4(2′-methoxyphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(14c) and 2,3,3aα,4α,6,7,11bβ,11cα-octahydro-2-methyl-4-(2′-methoxyphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15d). Prepared from 1,2,3,4-tetrahydroisoquinoline, 2-methoxybenzaldehyde and N-methylmaleimide in an analogous manner to that described above but with a reaction time of 3 h. Examination of the crude product (90%) by p.m.r. spectroscopy showed it to comprise a 2:1 mixture of (14c) and (15d), together with Michael adduct (12). Trituation of the gummy product with acetone followed by fractional crystallisation from acetone and benzene afforded pure samples of (14c), (15d) and (12). Careful examination of the mother liquors by p.m.r. and t.l.c. did not reveal any evidence of other stereoisomeric cycloadducts derived from the syn-dipole.

(14c) Colourless prisms from benzene, m.p. 223-225°C (Found: C, 72.8; H, 6.1; N, 7.85. $C_{22}H_{22}N_2O_3$ requires C, 72.9, H, 6.1; N, 7.75%); δ 2.43 and 2.72(2 x m, 2 x 1H, 2 x 7-H), 2.98(m, 2H, 2 x 6-H), 2.89(s, 3H, NMe), 3.60(d, 1H, 3a-H, J 7.6Hz), 3.77(t, 1H, 11c-H, J 7.8Hz), 3.90(s, 3H, OMe), 4.53(d, 1H, 11b-H, J 7.7Hz), 5.18(d, 1H, 4-H, J 0.9Hz) and 6.93-7.49 (m, 8H, ArH).

(15d) Colourless prisms from acetone, m.p. 210-212°C (Found: C, 73.05; H, 6.1; N, 7.65%); δ 2.35(m, 1H, 7-H), 2.89(s, 3H, NMe), 3.0(m, 1H, 7-H), 3.16(m, 2H, 2 x 6-H), 3.47(t, 1H, 3a-H, J 8Hz), 3.53(d, 1H, 11c-H, J 8Hz), 3.83(s, 3H, OMe), 4.77(d, 1H, 4-H, J 8Hz), 5.02(s, 1H, 11b-H) and 6.91-7.4(m, 8H, ArH).

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-,methyl-4(2′-propenyloxyphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(14d) and 2,3,3aα,4α,6,7,11bβ,11cα-octahydro-2-methyl-4-(2′-propenyloxphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15e). Prepared from 1,2,3,4-tetrahydroisoquinoline and 2-(2′-propenyloxy)-benzaldehyde in an analogous manner to that described above but with a reaction time of 3 h. The crude product (80%) was shown by p.m.r. spectroscopy to comprise a 2:1 mixture of (14d) and (15e) together with Michael adduct(12). Separation was achieved by a combination of flash chromatography eluting with 6:4 v/v ether-petroleum ether and fractional crystallisation. Careful examination of the mother liquours failed to reveal any cycloadduct derived from the syn-dipole.

(14d) Colourless rods from ethanol, m.p. 145-147°C (Found: C, 74.15; H, 6.2; N, 7.2. $C_{24}H_{24}N_2O_3$ requires C 74.2; H, 6.25; N, 7.2%); δ 2.44 and 2.70(2 x m, 2 x 1H, 2 x 7-H), 2.88(m + s, 4H, NMe and 6-H), 3.64(d, 1H, 3a-H, J 7.7Hz), 3.76(t, 1H, 11c-H, J 7.8Hz), 4.53(d, 1H, 11b-H, J 7.8Hz), 4.58 and 4.60(2 x d, 2 x 1H, CH_2O), 5.17(s, 1H, 4-H), 5.4(m, 2H, CH=C$\underline{H}_2$), 6.16(m, 1H, C$\underline{H}$=CH_2) and 6.91-7.47(m, 8H, ArH).

(15e) Colourless needles from methanol, m.p. 117-119°C (Found: C, 74.3; H, 6.15; N, 7.2. $C_{24}H_{24}N_2O_3$ requires C, 74.2; H, 6.25; N, 7.2%); δ 2.37(m, 1H, 7-H), 2.91(s, 3H, NMe), 2.95(m, 1H, 7-H), 3.15(m, 2H, 2 x 6-H), 3.5(t, 1H, 3a-H, J 8Hz), 3.54(d, 1H, 11c-H, J 8Hz), 4.63(m, 2H, CH_2O), 4.84(d, 1H, 4-H, J 8Hz), 5.04(s, 1H, 11b-H), 5.28(m, 2H, CH=C$\underline{H}_2$), 6.01(m, 1H, C$\underline{H}$=CH_2) and 6.91-7.41(m, 8H, ArH).

2,3,3aα,4β,6,7,11bα,11cα-Octahydro-2-methyl-4(2′-propargyloxyphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-

a]isoquinoline-1,3-dione(14e) and 2,3,3aα,4α,6,7,11bβ,11cα-octahydro-2-methyl-4(2′-propynyloxyphenyl)-1H-pyrrolo[3′,4′-3,4]pyrrolo[2,1-a]isoquinoline-1,3-dione(15f) Prepared from 1,2,3,4-tetrahydroisoquinoline and 2(2′-propynyloxy)-benzaldehyde in an analogous manner to that described above with a reaction time of 4h. The crude product (80%) was shown by p.m.r. spectroscopy to comprise a 2:1 mixture of (14e) and (15f) together with Michael adduct (12). Separation was achieved by a combination of flash chromatography and fractional crystallisation. Examination of the mother liquors failed to reveal any cycloadducts derived from the syn-dipole.

(14e) Obtained as a mixture with (15f). The p.m.r. data is extracted from the spectrum of the mixture. δ 2.44 and 2.71(2 x m, 2 x 1H, 2 x 7-H), 2.84-3.18(m, 2H, 2 x 6-H), 2.88(s, 3H, NMe), 3.64(d, 1H, 3a-H, J 7.7Hz), 3.8(t, 1H, 11c-H, J 7.7Hz), 4.53(d, 1H, 11b-H, J 7.7Hz), 4.79(s, 2H, CH_2O), 5.12(s, 1H, 4-H), and 6.97-7.47(m, 8H, ArH).

(15f) Colourless amorphous solid from dichloromethane, m.p. 184-187°C (Found: C, 74.45; H, 5.7; N, 7.1. $C_{24}H_{22}N_2O_3$ requires C, 74.6; H, 5.75; N, 7.25%); δ 2.35(m, 1H, 7-H), 2.47(t, 1H, ≡CH), 2.88(s, 3H, NMe), 3.00(m, 1H, 7-H), 3.16(m, 2H, 6-H), 3.50(t, 1H, 3a-H, J 8.1Hz), 3.53(d, 1H, 11c-H, J 8.0Hz), 4.74(d, 2H, CH_2O), 4.77(d, 1H, 4-H, J 8.3Hz), 5.02(s, 1H, 11b-H) and 6.99-7.39(m, 8H, ArH).

4bα,5,5aβ,11bβ,13,14-Hexahydro-6H-chromeno[3′,4′-4,5]pyrrolo[2,1-a]isoquinoline (20a) and 4bα,5,5aα,11bα,13,14-hexahydro-6H-chromeno[3′,4′-4,5]pyrrolo[2,1-a]isoquinoline (21). A solution of 1,2,3,4-tetrahydroisoquinoline (670mg, 5 mmol) and 2-(2′-propenyloxy)-benzaldehyde(810mg, 5 mmol) in xylene (50 ml) was boiled under reflux for 4 h. Work up in the usual way followed by flash chromatography afforded (20a) (660mg, 48%), m.p. 82-84°C, and (21)(170mg, 12%), m.p. 146-148°C. These cycloadducts were identified to those prepared previously via the decarboxylative route.[5]

6bα,8,9,14bβ,15,15aα-Hexahydro-1H-chromeno[3′,4′-2,3]indolizino[8,7-b]indole (22a) and 6bα,8,9,14bα,15,15aα-hexahydro-1H-chromeno[3′,4′-2,3]indolizino[8,7-b]indole (23). Prepared in an analogous manner to that described above from 1,2,3,4-tetrahydro-β-carboline (860 mg, 5 mmol) 2-(2′-propenyloxy)-benzaldehyde (810mg, 5 mmol) but with a reaction time of 24 h. Work up as above afforded (22a) (1.16g, 73%), m.p. 137-139°C, and (23) (80 mg, 5%), m.p. 210-212°C. These cycloadducts were identical to those prepared previously via the decaboxylative route.[5]

4bα,5,5aβ,11bβ,13,14-Tetrahydro-6H-chromeno[3′,4′-3,4]pyrrolo[1,2-a]isoquinoline (24). Prepared from 1,2,3,4-tetrahydroisoquinoline and 2-(2′-propynyloxy)-benzaldehyde in an analogous manner to that described above. The product (24) (65%), m.p. 156-158°C, was identified to that prepared previously via the decarboxylative route.[5]

Methyl 4bα,5α,5aβ,11bβ,13,14-hexahydro-6H-chromeno[3′,4′-4,5]pyrrolo[2,1-a]isoquinoline-5-carboxylate (20b). Prepared in analogous manner to that described above from 1,2,3,4-tetrahydroisoquinoline and 2-[(3′-carbomethoxy-2′-propenyl)oxy]-benzaldehyde. The reaction was carried out in boiling xylene for 2.5 h. Work up in the usual way afforded the *product* (60%), m.p. 142-144°C, as colourless rods from ether-petroleum ether. (Found: C, 75.1, H, 6.3; N, 4.15. $C_{21}H_{18}NO_3$ requires C, 75.2; H, 6.25; N, 4.2%); ν_{max} 2952, 1723, 1483, 1449, 1204, 1160 and 753 cm^{-1}; m/z(%) 335(M^+,43) 304(6), 276(5), 236(42), 205(76), 203(100), 145(55) and 131(51); δ 2.96(m, 3H, 13-H and

2 x 14-H), 3.29(m, 4H, OMe and 5aβ-H), 3.48(m, 1H, 13-H), 3.59(dd, 1H, 5α-H), 4.21 and 4.32(2 x dd, 2 x 1H, 2 x 6-H), 4.44(d, 1H, 4bα-H), 4.46(s, 1H, 11bβ-H) and 6.88-7.47(m, 8H, ArH); ^{1}H NOEDSY(%): irradiation of 5α-H caused enhancement of 4bα-H(11.5) and 6α-H(2). For formula numbering see reference 5.

Methyl 6bα,8,9,14bβ,15β,15aα-hexahydro-1H-chromeno[3′,4′-2,3]indolizino[8,7-b]indole-15-carboxylate (22b). Prepared in an analogous manner to that described above from 1,2,3,4-tetrahydro-β-carboline and 2-[(3′-carbomethoxy-2′-propenyl)oxy]-benzaldehyde. The reaction was carried out in boiling xylene for 3.5 h. Work up in the usual way afforded the *product* (57%) as colourless needles from ether, m.p. 221-223°C. The product was identified to that prepared previously via the decarboxylative route.[5]

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