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X=Y-ZH COMPOUNDS AS POTENTIAL 1,3-DIPOLES. PART 28.[1,2] THE IMINIUM ION ROUTE TO AZOMETHINE YLIDES. BACKGROUND AND REACTION OF AMINES WITH BIFUNCTIONAL KETONES.

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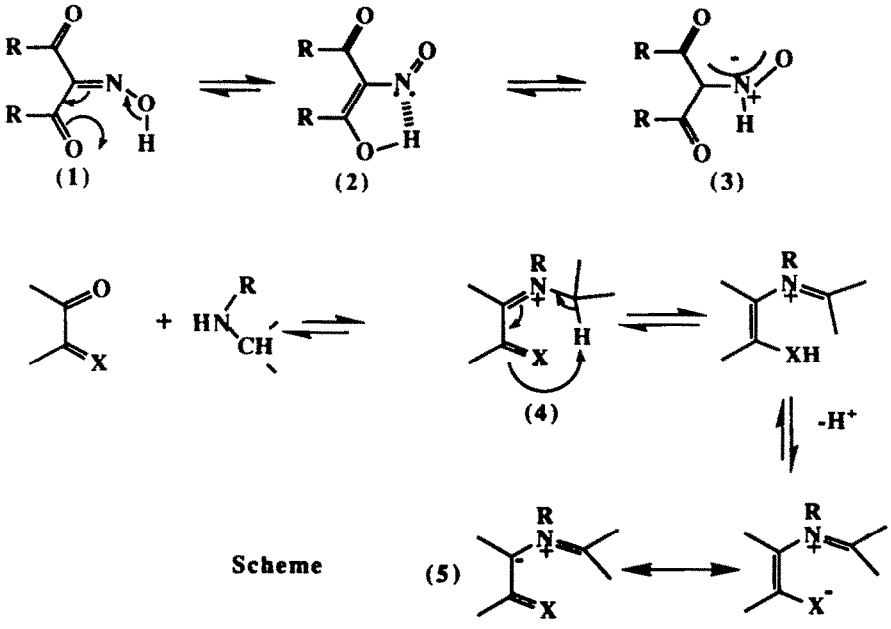
Abstract The reaction of isatin, ninhydrin and acenaphthenequinone with primary and secondary amines gives rise to stereospecific formation of intermediate azomethine ylides which can be trapped by cycloaddition to methyl acrylate or N-methylmaleimide. The regiochemistry of the cycloadditions to methyl acrylate is controlled by both frontier orbital and steric interactions with the latter dominating in the examples studied.

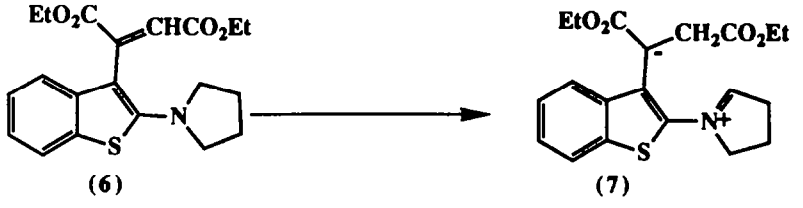
We have a general interest in developing new routes to 1,3-dipoles and have introduced several novel approaches to dipoles involving 1,2-prototropy,[3-6] decarboxylation of imines of α-amino acids,[7] nucleophilic processes involving the nitrogen lone pair of oximes,[8] and dehydrogenation of tertiary amines.[9] In earlier work with oximes[4] we utilised what we believe to be a 1,5-H shift (1) = (2) = (3) to generate an NH nitrone. The concept of a 1,5-H shift facilitating dipole formation led us to propose a related 1,5-H shift route to azomethine ylides(scheme).



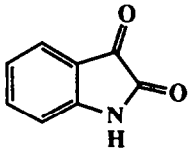
Scheme

We envisaged that unactivated primary and secondary amines would condense with suitable bifunctional carbonyl compounds to give intermediate iminium ions (4) (scheme) in which the charge might facilitate the 1,5-H shift (4, arrows). Sigmatropic i,j-rearrangements in charged systems are usually substantially faster than in the corresponding neutral systems and occur under mild conditions[10] although to our knowledge the concept of charge acceleration has not been applied to 1,5-shifts. However, Reinhoudt, in extensive studies, has reported the generation of 1,5-dipoles such as (7) via a 1,6-H shift in (6) and related systems.[11] The process outlined in scheme 1 results in the formation of a species (5) which could function as a 1,3- or 1,5-dipole.[12]

A survey of carbonyl compounds containing the moiety O=C-C=X showed a wide range of compounds were capable of generating azomethine ylides from primary and secondary amines. In selecting bifunctional compounds for evaluation we were greatly assisted by Schonberg and Moubasher's early work[13] on the Strecker degradation, a reaction which we recently showed involves azomethine ylide intermediates.[7,14] Thus isatin, ninhydrin, acenaphthenequinone, pyridine-2-carboxaldehyde, phenylglyoxal and ethyl glyoxalate all give rise to azomethine ylides. The bifunctional ketones isatin, ninhydrin and acenaphthenequinone are considered in this paper and the aldehydes in the succeeding paper.



(6) (7)



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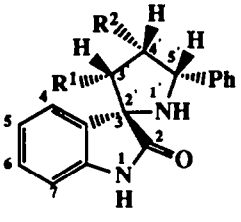
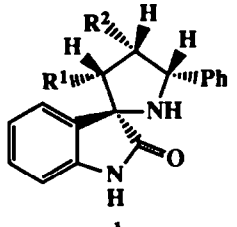
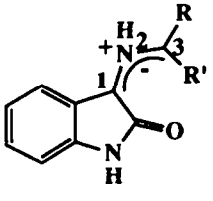


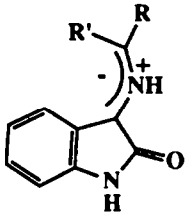
(9) a. $R^1=CO_2Me$, $R^2=H$
b. $R^1=H$, $R^2=CO_2Me$



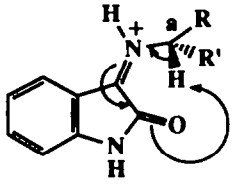
(10) a. $R^1=CO_2Me$, $R^2=H$
b. $R^1=H$, $R^2=CO_2Me$



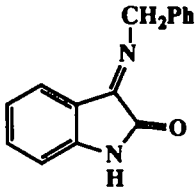
(11) a. R=Ph, R'=H
b. R=H, R'=Ph



(12) a. R=Ph, R'=H
b. R=H, R'=Ph



(13) a. R=Ph, R'=H
b. R=H, R'=Ph



(14)

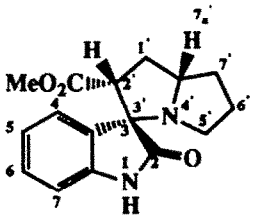
$CH_2=\overset{2}{C}H\overset{1}{C}O_2Me$

(15)

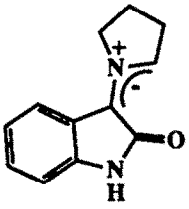
a. Isatin. Early work by Schonberg et al. had shown that benzylamine is converted into benzaldehyde on reaction with isatin.[13] This encouraged us to heat a mixture of isatin(8), benzylamine, and methyl acrylate in boiling acetonitrile for 6 h when we observed the formation of a 5:2 mixture (60%) of the regioisomeric cycloadducts (9a) and (9b). The regiochemistry of (9a) and (9b) was apparent from the multiplicity of the 5′-H signal in their ^{1}H n.m.r. spectra. Thus in (9a) this proton gives rise to a double doublet whilst in (9b) the proton signal is a doublet. The cis-stereochemistry of the 3′-H, 4′-H and 5′-H protons of (9a) and (9b) was established by n.O.e. experiments ($CDCl_3$) (see experimental section). The stereochemistry of the products at the C(2) quaternary centre could not be firmly established and is provisionally assigned on the basis of comparisons with selected cycloadducts (see below) and on mechanistic interpretation.[15] Condensation of benzylamine with isatin could give rise to four configurationally distinct azomethine ylides (11a,b) and (12a,b). Azomethine ylides (11a) and (11b) could arise via a 1,5-H shift in (13a) and (13b) respectively, with accompanying flattening at centre a as the hybridisation of the centre changes from sp^3 to sp^2. The transition state leading to azomethine ylide (11a) is favoured over that leading to (11b) due to the developing steric clash between the carbonyl moiety and the phenyl group in the latter case. Azomethine ylides (12a) and (12b) cannot arise via Scheme 1 but could arise by deprotonation of imine (14). In this case (12a) is energetically favoured over (12b) due again to steric effects. Assuming for the moment that the kinetically formed dipole has configuration (11a), then (9a) and (9b) arise via endo- transition states. The regioselectivity for (9a) presumably reflects a concerted but non-synchronous transition state in which 4,5-bond formation is in advance of 2,3-bond formation for (9a) and vice-versa for (9b). The formation of both (9a) and (9b) indicates that the reduced steric hindrance at the singly substituted azomethine ylide terminus is comparable to, but slightly outweighs, the more favourable orbital interaction between C(1) (dipole HOMO) of (11a) and C(2) (dipolarophile LUMO) of (15) usually observed in this type of system.[16,17]

In contrast the reaction of pyrrolidine, isatin, and methyl acrylate (MeCN, 80°C, 3h) occurs regio- and stereo-specifically giving (16) (69%). The relative stereochemistry of the 2′-H and 7a′-H protons was

again established by n.O.e. studies, whilst the stereochemical assignment at C(2) was initially provisional[2] but has recently been confirmed by a single crystal X-ray structure (figure). The product thus arises from azomethine ylide (17) via an endo-transition state with the regiospecificity reflecting dominating steric effects in the transition state as discussed above.



(16)



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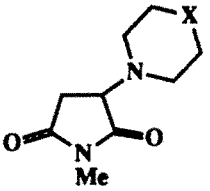
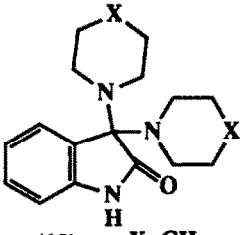
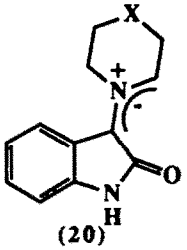


(18) a. X=CH_2
b. X=S
c. X=NMe
d. X=O



(19) a. X=CH_2
b. X=S
c. X=NMe
d. X=O



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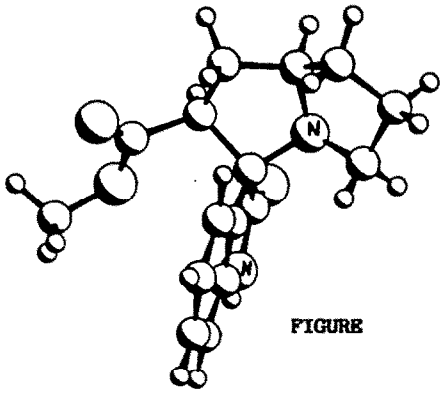


FIGURE

Crystal Data for(16) $C_{16}H_{18}O_3N_2$. M = 286.3, orthorhombic, a = 8.312(2), b = 21.392(4), c = 17.030(4) Å, U = 3028.1 $Å^3$, Z = 8, Dx = 1.26 g cm^{-3}, F(000) = 1216, space group $Pca2_1$(no. 29), Mo-Kα radiation, λ = 0.71073 Å, μ(Mo-Kα) = 0.52 cm^{-1}. Siemens P3/V2000 diffractometer, $3 \leq 2\theta \leq 50°$, θ/2θ scans, 3048 unique measured data, 2763 with I>O. Analysis (by the direct methods of SHELX86) and least squares refinement (SHELX76) established the space group as $Pca2_1$ (with two crystallographically independent, though chemically equivalent, molecules in the asymmetric unit) rather than Pcam (alt. Pbcm, no. 57). Non-H atoms anisotropic; all hydrogens located in a difference Fourier

synthesis but only the hydrogens on the pyramidal nitrogens were refined freely; all other hydrogens riding on carbons (C-H = 1.08 Å); common isotropic vibration parameters, Uiso, for methyl, methylene, tertiary -CH and aromatic hydrogens refined to values of 0.084(13), 0.099(6), 0.084(9) and 0.083(7) respectively. Final R = 0.042, Rw = 0.045 for 2236 data with $F>6\sigma(F)$. Weighting scheme $w = 2.13/[\sigma^2(F) + 0.00059F^2]$.[18]

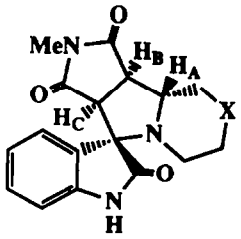
Attempts to carry out analogous reactions to that of pyrrolidine by reacting isatin with piperidine, N-methylpiperazine, morpholine or thiomorpholine, using N-methylmaleimide as the dipolarophile gave disappointing results. The major product in each of these cases was the N-Michael adduct (18). However, it proved possible to utilise this facile Michael addition process by preparing the 3,3-diaminooxindoles (19a-d) and reacting these compounds with two mols of N-methylmaleimide in boiling toluene. Under these conditions an easily separable 1:1 mixture of Michael adduct (18) and cycloadduct was produced in essentially quantitative yield. In each case the cycloadducts are believed to arise from azomethine ylide (20). The cycloadducts are predominantly or exclusively derived via an exo-transition state i.e. (21). In some cases substantial amounts of the corresponding endo-isomer (22) were also formed (Table). Endo-exo stereochemistry is assigned on the basis of n.O.e. studies. In particular irradiating H_A in (21) and (22) produces enhancements of ca. 1% in the signal for H_B in (21) and ca. 8% in (22). Stereochemistry at the spiro-centre is assigned on the basis of that established for (16).

Table. Endo- and exo-cycloadducts derived from the reaction of 3,3-diaminooxindoles (19a-d)(1 mol) with N-methylmaleimide (2 mol).[a]

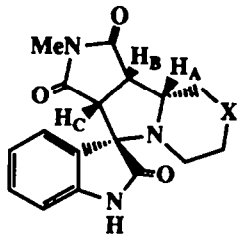
3,3-Diaminoxindole	Time(h)	Product(ratio)		Combined Yield(%)[b]
		exo	endo	
19a	23	21a	-[c]	89
19b	3	21b(2)	22b(1)	90
19c	5.25	21c(2.7)	22c(1)	87
19d	15	21d	-[d]	88

a. All reactions carried out in boiling toluene.
b. Estimated by 'H n.m.r.
c. Trace of endo-isomer (22a) is produced.
d. No endo-isomer (22d) could be detected.

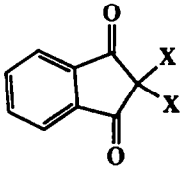
b. Ninhydrin. The reaction of ninhydrin (23a) with primary α-amino acids results in the formation of a purple dye Ruhemann's Purple. We have recently shown that this reaction involves two types of azomethine ylide both of which can be trapped in cycloaddition reactions with N-methylmaleimide.[19] Moreover, we demonstrated that protonated Ruhemann's Purple (24), the product of the reaction of Ruhemann's Purple (a sodium or ammonium salt), and hydrochloric acid is a stable NH azomethine

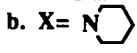


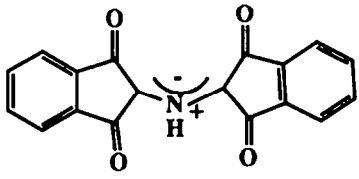
(21) a. X=CH_2
b. X=S
c. X=NMe
d. X=O



(22) a. X=CH_2
b. X=S
c. X=NMe
d. X=O



(23) a. X=OH
b. X= 



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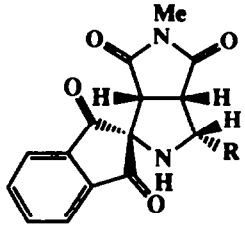
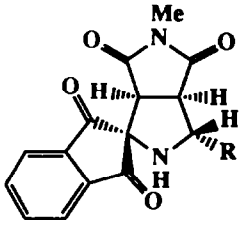
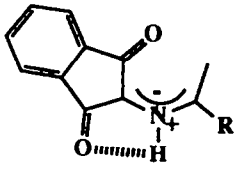


(25) a. R=p-MOC_6H_4
b. R=3-pyridyl



(26) R=p-$MeOC_6H_4$



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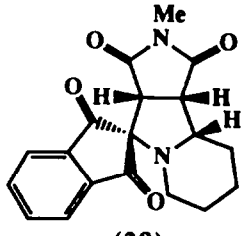

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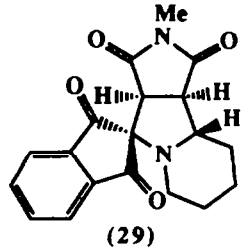
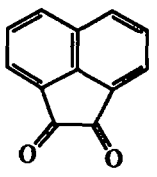


(29)

ylide.[19,20] Thus we anticipated that the reaction of primary and secondary amines with ninhydrin would also furnish azomethine ylides.

On heating a mixture of ninhydrin (23a), 4-methoxybenzylamine and N-methylmaleimide in acetonitrile (80°C, 24h), reaction occurred to furnish a 7.7:1 mixture of endo- and exo-cycloadducts (25a) and (26), respectively, in a combined yield of 73%. An analogous reaction using 3-aminomethylpyridine as the amine component gave a single product (25b), arising from endo-addition of the dipolarophile, in 72% yield. Again n.O.e. studies were used to assign stereochemistry. Since ninhydrin has two carbonyl groups flanking the reacting centre the designation endo- and exo- refers to the stereochemistry with respect to the R substituent in (27) which is ajudged to be the dipole formed under kinetic control, on steric grounds.[19] One reaction of ninhydrin with a secondary amine, piperidine, was studied. Again it was found advantageous in terms of yield of cycloadduct to utilise the dipiperidinyl compound (23b) and two mol. of N-methylmaleimide otherwise the N-Michael adduct (18, X=CH_2) predominated. Using this approach the reaction (toluene, 110°C, 6h) gave a near quantitative yield of a 1:1 mixture of Michael adduct (18, X=CH_2) and cycloadducts (28) and (29). The endo- and exo- cycloadducts (28) and (29) were obtained as a 1:1 mixture and their stereochemistry is assigned on the basis of n.O.e. studies (see experimental section).

c. **Acenaphthenequinone.** The reaction (MeCN, 80°C) of acenaphthenequinone (30) with N-methylmaleimide and either 4-methoxybenzylamine or 3-aminomethylpyridine gave a single cycloadduct, (31a)(67%) and (31b)(63%) respectively, in each case. Cycloadduct stereochemistry, apart from the spiro-centre, is assigned on the basis of n.O.e. studies (see experimental section). Stereochemistry at the spiro centre is provisionally assigned on the basis that the dipole involved has configuration (32).



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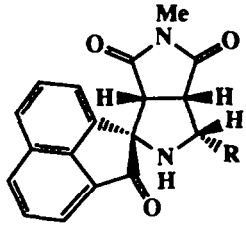
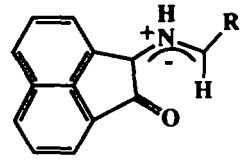


(31) a. R=p-$MeOC_6H_4$
b. R=3-pyridyl



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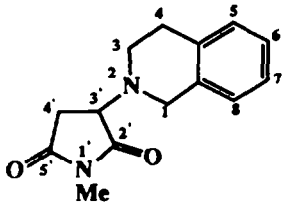

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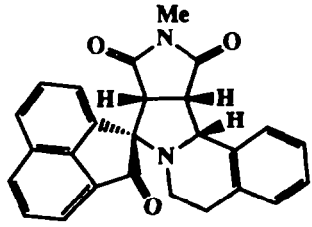
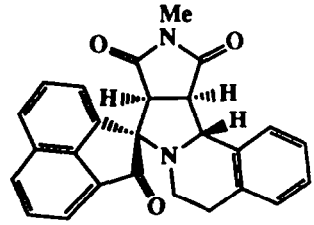


(34)



(35)

One example of the reaction of (30) with a secondary amine, 1,2,3,4-tetrahydroisoquinoline, was studied. Heating a 1:1:1 molar mixture of (30), N-methylmaleimide and 1,2,3,4-tetrahydroisoquinoline in boiling toluene gave mainly Michael adduct (33). However, when (30) and 1,2,3,4-tetrahydroisoquinoline were heated in boiling toluene for 40 min. and then N-methylmaleimide added and heating continued for a further 2h, a 1:1 mixture of endo- and exo- cycloadducts, (34) and (35) respectively, was obtained in 55% yield. Thus formation of (34) and (35) involves regiospecific azomethine ylide formation at the benzylic site of the tetrahydroisoquinoline. Cycloadduct stereochemistry is assigned on the same basis as discussed above for (31).

The dipole stereochemistry inherent in cycloadduct (16) accords with that expected for a 1,5-H shift mechanism. However, studies utilising monofunctional aryl aldehydes as the carbonyl component also result in dipole formation. The mechanistic implications of these observations are discussed in the accompanying paper,[15] together with dipole formation from bifunctional aldehydes.

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).

Isatin cycloadducts.

2,2′,3,3′α,4′,5′α-Hexahydro-3′-methoxycarbonyl-5′-phenylspiro[indole-3,2′-pyrrole]-2-one(9a) and 2,2′,3,3′,4′α,5′α-hexahydro-4′-methoxycarbonyl-5′-phenylspiro[indole-3,2′-pyrrole]-2-one(9b). A solution of isatin(740mg, 5 mmol), benzylamine(540 mg, 5 mmol) and methyl acrylate(5 mmol) in acetonitrile(50 ml) was boiled under reflux for 6 h. The solvent was then evaporated under reduced pressure and the residue separated by flash chromatography eluting with ether-petroleum ether to afford (9a)(690 mg, 43%) and (9b)(280 mg, 17%)

(9a) Colourless prisms (ethanol), m.p. 136-137°C (Found: C, 70.75; H, 5.7; N, 8.75. $C_{19}H_{18}N_2O_3$ requires C, 70.8; H, 5.65; N, 8.7%); ν_{max} 3400, 3000, 1705, 1655, 1430 and 760 cm^{-1}; m/z(%) 322 (M^+,85), 294(50), 291(7), 263(33), 261(22), 245(2), 235(42) and 119(100); δ2.37(s, 1H, NH), 2.54(m, 2H, 4′-H), 3.20(s, 3H, OMe), 3.69(dd, 1H, 3′-H, J 7.91, 11.03Hz), 4.84(dd, 1H, 5′-H, J 6.39, 9.91Hz), 6.89-7.53(m, 9H, ArH) and 9.13(s, 1H, NH); ^{1}H NOESDY (%): irradiation of 3′-H caused enhancements of 5′-H (5) and 4′-H (4); irradiation of 5′-H caused enhancements of 3′-H (8), 4′-H (4) and ArH (11).

(9b) Colourless rods (ethanol), m.p. 177-178°C (Found: C, 70.65; H, 5.75; N, 8.85); ν_{max} 3330, 3180. 1730, 1700, 1615, 1470 and 755 cm^{-1}; m/z(%) 322 (M^+,15), 294(10), 290(16), 263(1), 235(100) and 177(57); δ2.49(dd, 1H, 3′β-H, J 8.30, 11.54Hz), 2.66(dd, 1H, 3′α-H, J 5.90, 13.56Hz), 3.21(s, 3H, OMe), 3.81(ddd, 1H, 4′-H), 5.36(d, 1H, 5′-H, J 8.43Hz), 6.87-7.77(m, 9H, ArH) and 8.05(s, 1H, NH); ^{1}H NOESDY (%): irradiation of 4′-H caused enhancements of 5′-H (10) and 3′-H (6); irradiation of 5′-H caused enhancements of 4′-H (15) and ArH (17).

2,2′α,3,3′,5′,6′,7′,7a′α-Octahydro-2′methoxycarbonyl-spiro[indole-3,3′-pyrrololizidine]-2-one(16). Prepared as above from isatin (740 mg, 5 mmol), pyrrolidine (360 mg, 5 mmol) and methyl acrylate (430 mg, 5 mmol) in MeCN (50 ml). Heating was continued for 3 h. T.l.c., eluting with 7:3 v/v ethyl acetate-

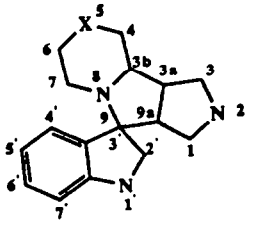
petroleum ether showed one spot with R_f 0.21. The product was purified by flash chromatography to give (16) (990mg, 69%) which crystallised from ethanol as colourless prisms, m.p. 178-180°C (Found: C, 66.9; H, 6.5: N, 9.85. $C_{16}H_{18}N_2O_3$ requires C, 67.1; H, 6.35; N, 9.8%); ν_{max} 1730, 1620, 1470, 1210, 760 and 740 cm^{-1}; m/z(%) 286 (M^+, 50), 258(30), 255(7), 277(22) and 199(100); δ1.50-2.69(m, 8H, 1′-, 5′-, 6′- and 7′-H), 3.22(s, 3H, OMe), 3.83-3.91(dd, 1H, 2′-H, J 6.81 and 12.91Hz), 4.02-4.14(m, 1H, 7a′-H), 6.93-7.30(m, 4H, ArH) and 9.70 (s, 1H, NH); ^{1}H NOESDY (%): irradiation of 2′-H caused enhancements of 1′α-H (5) and 7a′-H (2); irradiation of 7a′-H caused enhancements of 2′-H (5) and 1′α- and 7′α-H combined (7).

3,3-Diaminooxindoles. Compounds (19a) and (19d) were prepared according to Johnson and McCaldin.[22]

3,3-Di(4-thiomorpholino)oxindole (19b). Prepared using a modification of the general method of Johnson and McCaldin.[22] A solution of isatin (1.47g, 10 mmol) and thiomorpholine (2.06g, 20 mmol) in ethanol (16 ml) was boiled under reflux for 1.5 h. The reaction mixture was cooled and filtered. The residue was washed with cold ethanol to afford the product as a colourless powder (1.84g, 55%), m.p. 187-188°C (Found: C, 57.1; H, 5.9; N, 12.3 %. $C_{16}H_{21}N_3OS_2$ requires C, 57.3; H, 6.25; N, 12.55%); m/z (%) 334(M^+-1, 0.5), 262(2), 248(2), 235(4), 234(23), 233(32), 232(58), 178(8), 133(32), 132(48), 131(5), 118(9), 105(7), 104(17), 103(100), 102(18), 101(44), 100(45) and 88(18). The compound was too insoluble for n.m.r. studies.

3,3-Di(N-methylpiperazino)oxindole(19c). A solution of isatin (1.47g, 10 mmol) and N-methylpiperazine (2.0g, 20 mmol) in methylene chloride (20ml) containing $MgSO_4$ (3.2g) was stirred at room temperature for 1.75 day. The reaction mixture was filtered to remove the $MgSO_4$ and the filtrate evaporated. The residue was crystallised from methylene chloride-ether to afford pale yellow prisms (2.0g, 61%) of the 3,3-di(N-methylpiperazino)oxindole, m.p. 153-155°C (Found: C, 62.5; H, 7.9; N, 19.7. $C_{18}H_{27}N_5O.H_2O$ requires C, 62.25; H, 8.35; N, 20.15%); m/z (%) 329(M^+, 0.5), 328(2), 232(8), 231(57), 230(100), 133(18), 132(10), 100(46), 99(100), 98(19), 97(34), 85(14), 71(11) and, 70(38); δ7.2 (m, 2H, ArH), 6.9(t, 1H, ArH), 6.8(d, 1H, ArH), 2.8(broad s, 8H, 4 x NCH_2), 2.4(broad s, 8H, 4 x N(Me)CH_2), and 2.2(s, 6H, 2 x CH_3).

Reaction conditions and yields of products from cycloadditions of the 3,3-diaminooxindoles are collected in the table.



1,1′,2,3,3a,3b,4,5,6,7,9,9a-Dodecahydro-9-(spiro-3′-indolino)-pyrrolo[c-3,4]indolizine skeleton (X=CH_2).

Cycloadduct and Michael adduct from 3,3-dipiperidinooxindole. A solution of 3,3-dipiperidinooxindole

(19a)(900 mg, 3 mmol)[22] and N-methylmaleimide (670 mg, 6 mmol) in dry toluene (14 ml) was boiled under reflux for 23.5 h. N.m.r. monitoring showed the formation of Michael adduct and two cycloadducts (mainly exo-isomer). The solvent was evaporated to leave a brown residue (1.39g, 89%), which comprised a 1:1 mixture of Michael- and cyclo-adducts. The products were separated by fractional crystallisation from toluene and from methanol. The minor cycloadduct was only present in trace amount.

1,1′,2,3,3aα,3bβ,4,5,6,7,9,9aα-Dodecahydro-9-(spiro-3′-indolino-2′-one)-2-methyl-1,3-dioxopyrrolo[c-3,4]indolizine (21a). Colourless cubic plates (from methanol) m.p. 271-273°C (Found: C, 66.6; H, 5.4; N, 12.9. $C_{18}H_{19}N_3O_3$ requires C, 66.45; H, 5.85; N, 12.9%); m/z(%) 325(M^+, 100), 297(12), 296(31), 267(9) and 193(11); δ 7.8(s, 1H, NH), 7.30(m, 2H, ArH), 7.1(t, 1H, ArH), 6.80(d, 1H, ArH), 3.60(d, 1H, 9a-H), 3.50(m, 1H, 3b-H), 3.20(t, 1H, 3a-H), 3.00(s, 3H, CH_3), 2.20-2.40(m, 3H, 7-CH_2, 4-H), 1.80(m, 1H, 4-H) and 1.30-1.60(m, 4H, 5-CH_2, 6-CH_2); ^{1}H NOEDSY(%): irradiation of 3a-H caused enhancement of 9a-H(14); irradiation of 3b-H caused enhancements of 3a-H(1) and 4-H(9).

N-[3-(2′,5′-Dioxo-1′-methyl-pyrrolidinyl)]piperidine(18a). Colourless needles (from chloroform/petroleum ether) m.p. 44-46°C (Found: N, 14.0. $C_{10}H_{16}N_2O_2$ requires N, 14.3%); m/z (%) 196(M^+, 9), 195(72), 111(6), 110(13), 85(8) and 84(100); δ3.80(dd, 1H, 3-H), 3.00(s, 3H, NCH_3), 2.78(m, 4H, CH_2NCH_2), 2.43(dd, 2H, 4-CH_2), 1.65(q, 4H, 2 x CH_2) and 1.49(q, 2H, CH_2).

Cycloadducts and Michael adduct from 3,3-di(4-thiomorpholino)oxindole. A solution of 3,3-di(4-thiomorpholino)oxindole(19b)(670 mg, 2 mmol) and N-methylmaleimide (440 mg, 4 mmol) in dry toluene (15 ml) was boiled under reflux for 3 h. N.m.r. monitoring showed a 1:1 mixture of Michael adduct and cycloadducts. The cycloadducts comprised a 2:1 mixture of exo-(21b)- and endo-(22b)-isomers (as estimated by p.m.r.). The reaction mixture was evaporated and the solid residue (1.0g, 90%) was then crystallised from a mixture of methanol and a little toluene. Two kinds of crystals were obtained: the major cycloadduct formed pale yellow prisms and the minor cycloadduct crystallised as chunky cream prisms. These were separated using tweezers. The Michael adduct was isolated by fractional crystallisation of the residue obtained from the filtrate.

(21b) Pale yellow prisms from methanol, m.p. 265-267°C [Found (mixed isomers): C, 59.3; H, 5.3; N, 12.55. $C_{17}H_{17}N_3O_2S$ requires C, 59.5; H, 5.0; N, 12.25%]; m/z (%) 343(M^+, 100), 314(23), 282(10), 269(17), 258(10), 242(20), 211(17), 185(19), 184(15), 141(13) and 102 (13); δ8.45(broad s, 1H, NH), 7.25(m, 2H, ArH), 7.10(t, 1H, ArH), 6.80(d, 1H, ArH), 3.80(m, 1H, 3b-H), 3.55(d, 1H, 9a-H), 3.20(t, 1H, 3a-H), 3.00(m, 2H, 4-H, 7-H), 2.95(s, 3H, NMe), 2.60-2.80(m, 3H, 4-H, 6-H and 7-H) and 2.30(m, 1H, 6-H); ^{1}H NOEDSY (%): irradiation of 3b-H caused enhancements of 3a-H(1), 4-H and 7-H combined (4) and 6H(2); irradiation of 9a-H caused enhancement of ArH(5), 3a-H(6) and 3b-H(0.5); irradiation of 3a-H caused enhancements of 9a-H(7), 4-H(3.5), 3b-H(1) and ArH(1).

(22b) Chunky cream prisms from methanol, m.p. 255-257°C. δ8.35(broad s, 1H, NH), 7.25, 7.05 (2 x t, 2 x 1H, ArH), 6.85(d, 1H, ArH), 6.80(d, 1H, ArH), 4.05(m, 1H, 3b-H), 3.60(t, 1H, 3a-H), 3.40(d, 1H, 9a-H), 3.45(broad d, 1H, 7-H), 3.05(s, 3H, NMe), 2.95(q, 1H, 4-H), 2.70(q, 1H, 4-H), 2.6(m, 2H, 6-H and 7-H) and 2.3(m, 1H, 6-H); ^{1}H NOEDSY(%): irradiation of 3b-H caused enhancements of 3a-H(8),

9a-H(0.5), 4-H(4) and 7-H(4); irradiation of 9a-H caused enhancements of 3a-H(b) and 3b-H(1); irradiation of 3a-H caused enhancements of 3b-H(7), 9a-H(7) and 4-H(1).

N-[3-(2′,5′-Dioxo-1′-methyl-pyrrolidinyl)]-thiomorpholine. (18b). Colourless prisms (chloroform/petroleum ether m.p. 122-124°C (Found C, 50.2; H,6.85; N, 13.35. $C_9H_{14}N_2O_2S$ requires C, 50.45; H, 6.6; N, 13.1%); m/z (%) 214(M^+, 59), 199(3), 167(15), 114(31), 113(100), 112(6) and 102 (96); δ 3.85(dd, 1H, 3-H), 3.00(s, 3H, NCH_3) and 2.70-2.90(m, 10H, 5 x CH_2).

Cycloadducts and Michael adduct from 3,3-di(N-methylpiperazino)oxindole. A solution of 3,3-di(N-methylpiperazino)oxindole(19c)(330 mg, 1 mmol) and N-methylmaleimide (220 mg, 2 mmol) in dry toluene (9 ml) was boiled under reflux for 5.25 h. Evaporation of the solvent gave a yellow solid (480 mg, 87%) containing a 1:1 mixture of Michael adduct and cycloadducts. The cycloadduct comprised a 2.7:1 mixture of exo-(21c) and endo-(22c) isomers (as estimated by p.m.r.). The Michael adduct and cycloadducts were separated by flash chromatography (CH_2Cl_2/MeOH, 25:1). A pure sample of the exo-isomer was isolated (140 mg, 41%) but the endo-isomer was contaminated by the Michael adduct. (21c) Colourless needles (from methanol/hexane), m.p. 263-265°C (Found: C, 63.4; H, 6.05; N, 15.95. $C_{18}H_{20}N_4O_3$ requires C, 63.55, H, 5.9; N, 16.45%) m/z (%) 340(M^+, 52), 247(51), 209(20), 149(18), 127(18), 120(89), 99(38), 98(30), 92(20), 86(23), 84(37) and 70(100); δ8.60(broad s, 1H, NH), 7.25(m, 2H, ArH), 7.05(t, 1H, ArH), 6.80(d, 1H, ArH), 3.75(m, 1H, 3b-H), 3.60(d, 1H, 9a-H), 3.30(broad d, 1H, 4-H), 3.15(t, 1H, 3a-H), 2.95(s, 3H, NMe), 2.65(broad d, 1H, 6-H), 2.45(m, 1H, 7-H), 2.30(s, 3H, NMe), 2.25(m, 2H, 6-H, 7-H) and 2.00(t, 1H, 4-H); ^{1}H NOEDSY(%): irradiation of 3b-H caused enhancement of 4-H(2), 3a-H(1) and 7-H(4); irradiation of 9a-H caused enhancements of 3a-H(6) and ArH(4); irradiation of 4-H caused enhancement of 3b-H(4) and 4-H(12); irradiation of 3a-H caused enhancement of 9a-H(8), 3b-H(1) and 4-H(3).

(22c). The p.m.r. data (below) were obtained from a mixture with the Michael adduct. δ8.81(broad s, 1H, NH), 7.28(t, 1H, ArH), 7.04(t, 1H, ArH), 6.87(d, 1H, ArH), 6.77(d, 1H, ArH), 4.0(m, 1H, 3b-H), 3.50 (d, t, 2H, 3a-H, 9a-H), 3.27(broad d, 1H, 4-H), 3.10(s, 3H, NMe), 2.50(m, 1H, 7-H), 2.31(s, 3H, NMe) and 2.20-1.95(m, 3H, 4-H, 6-H, 7-H).

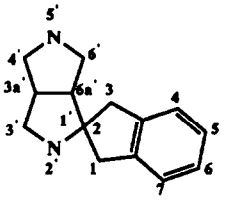
N-[3-(2′,5′-Dioxo-1′-methyl-pyrrolidinyl)]-N-methylpiperazine (18c). Colourless prisms from chloroform/petroleum ether, m.p. 73-75°C (Found: C, 57.1; H, 7.9; N, 20.2. $C_{10}H_{17}N_3O_2$ requires C, 56.85; H, 8.1; N, 19.9%); m/z (%) 211(M^+, 77), 112(100), 71(30) and 70 (55); δ 3.81(dd, 1H, 3-H), 3.00(s, 3H, NMe), 2.78(m, 4H, 2 x NCH_2), 2.50(m, 6H, 2 x N(Me)CH_2 and CH_2CO) and 2.28(s, 3H, NMe).

Cycloadducts and Michael adduct from 3,3-di(4-morpholino)oxindole 3,3-Di(4-morpholino)oxindole (19a)[22] (1.515g, 5 mmol) and N-methylmaleimide (556 mg, 5 mmol) in dry toluene (30 ml) were boiled under reflux for 1.25 h. Evaporation of the reaction mixture afforded a brown solid (1.82g, 88%) whose p.m.r. spectrum showed it to comprise of a 1.7:1 mixture of the exo-cycloadduct (21d) and Michael adduct (18d) together with a trace of another compound (probably the endo-cycloadduct). Crystallisation of the solid from methanol containing a little toluene gave the major cycloadduct (21d). When two mol of N-methylmaleimide were used to one mol of 3,3-di(4-morpholino)oxindole a 1:1 mixture of Michael adduct and cycloadduct (79%) was obtained.

(21d) Colourless prisms from methanol-toluene, m.p. 288-289°C(Found: C, 61.8: H, 5.25; N, 13.45. $C_{17}H_{17}N_3O_4$ requires C, 62.35; H, 5.25; N, 12.85%); m/z (%) 327(M^+, 100), 326(11), 299(27), 298(55), 269(50), 268(17), 242(11), 241(10), 211(28), 194(11), 185(17), 184(37), 183(17), 169(15), 158(17) and 130(15); δ(assignments made in conjunction with ^{1}H COSY spectrum) 7.80(broad s, 1H, NH), 7.28(d, 1H, ArH), 7.27 and 7.10(2 x t, 2 x 1H, ArH), 6.82(d, 1H, ArH), 4.3(dd, 1H, 4-H), 3.76(m, 1H, 6-H), 3.75(dd, 1H, 3b-H), 3.62(d, 1H, 9a-H, J9.75 Hz), 3.37(m, 2H, 4-H and 6-H), 3.14(t, 1H, 3a-H, J9 Hz), 2.97(s, 3H, NCH_3), 2.56(sextet, 1H, 7-H), 2.23 (broad dd, 1H, 7-H); ^{1}H NOEDSY (%): irradiation 9a-H caused enhancements of ArH(4) and 3a-H(7); irradiation of 3a-H caused enhancement of 3b-H(1), 9a-H(8), cis-4-H(3) and trans-4-H(1).

N-[3-(2′,5′-Dioxo-1′-methyl-pyrrolidinyl)]morpholine (18d). Pale yellow prisms from toluene, m.p. 89-90°C (Found: C, 55.2; H, 7.1; N, 14.0. $C_9H_{14}N_2O_3$ requires C, 54.55; H, 7.05; N, 14.15%); m/z(%) 198 (M^+, 12), 167(3), 155(10), 113(44) and 86(100); δ 3.8(q, t; 5H, NCH, 2 x OCH_2), 3.0(s, 3H, NMe), 2.9-2.7(m, 4H, 2 x NCH_2) and 2.5(q, 2H, CH_2).

Ninhydrin Cycloadducts



1′,2,3,3′,3a′,4′,6′,6a′-Octahydrospiro[indene-2,1′-pyrrolo[3,4-c]pyrrole] skeleton.

1′,2,3,3′α,3a′α,4′,6′,6a′α-Octahydro-3′-(4-methoxyphenyl)-5′-methylspiro[indene-2,1′-pyrrolo[3,4-c]pyrrole]-1,3,4′,6′-tetraone(25a) and 1,2′,3,3′α,3a′β,4′,6′,6a′β-octahydro-3′-(4-methoxyphenyl)-5′-methylspiro[indene-2,1′-pyrrolo[3,4-c]pyrrole]-1,3,4′,6′-tetraone(26).

A solution of ninhydrin (890mg, 5 mmol) and 4-methoxybenzylamine(690mg, 5 mmol) in MeCN (50ml) was boiled under reflux for 24 h. T.l.c., eluting with 7:3 v/v chloroform-ether, showed two spots, R_f 0.65 and 0.51. The isomers were separated by prep. t.l.c. to give (26) (160mg, 8%) and (25a) (1.27g, 65%).

(25a) Pale yellow rods (chloroform-petroleum ether) m.p. 229-230°C. (Found: C, 67.85; H, 4.6; N, 6.95. $C_{22}H_{18}O_5N_2$ requires C, 67.7; H, 4.65; N, 7.2%); ν_{max} 3320, 2900, 1690, 1500, 1240 and 915 cm^{-1}; m/z(%) 390 (M^+, 100), 389(15), 279(52), 121(51), 105(33) and 77(31); δ 2.97(s, 3H, NMe), 3.48(d, 1H, 6a′-H, J 7.79Hz), 3.70(t, 1H, 3a′-H, J 7.83Hz), 3.82(s, 3H, OMe), 5.42(d, 1H, 3′-H, J 8.02Hz), 6.91(m, 2H, ArH), 7.33(m, 2H, ArH) and 7.94-8.12(m, 4H, ArH); ^{1}H NOESDY (%): irradiation of 6a′-H caused enhancement of 3a′-H (16); irradiation of 3a′-H caused enhancements of 6a′-H (13) and 3′-H (14); irradiation of 3′-H caused enhancements of 3a′-H (18) and ArH (18).

(26) Pale yellow plates (chloroform-petroleum ether) m.p. 183-184°C. (Found: C, 67.7, H, 4.55; N, 7.2. $C_{22}H_{18}O_5N_2$ requires c, 67.7, H, 4.65; N, 7.2%); ν_{max} 3280, 2920, 1695, 1510, 1280 and

820 cm^{-1}; m/z(%) 390(M^+, 100), 389(11), 279(28), 121(29), 105(21) and 77(17); δ 2.66(d, 1H, NH, J 8.48Hz), 3.00(s, 3H, NMe), 3.60(dd, 1H, 3a′-H, J 7.71 and 9.86Hz), 3.81(s, 3H, OMe), 3.89(d, 1H, 6a′-H, J 9.78Hz), 4.98(t, 1H, 3′-H, J 7.83Hz), 6.92(m, 2H, ArH), 7.49(m, 2H, ArH), 7.90-8.09(m, 4H, ArH); ^{1}H NOESDY (%): irradiation of 6a′-H caused enhancement of 3a′-H (20); irradiation of 3a′-H caused enhancement of 6a′-H (28), 3′-H (4) and ArH(8); irradiation of 3′-H caused enhancements of 3a′-H (3) and ArH (13).

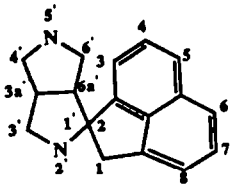
1′,2,3,3′α,3a′α,4′,6′,6a′α-Octahydro-5′-methyl-3′-(3-pyridyl)spiro[indene-2,1′-pyrrolo[3,4-c]pyrrole]-1,3,4′,6′-tetraone (25b). A solution of ninhydrin (890 mg, 5 mmol), 3-aminomethylpyridine (540 mg, 5 mmol) and N-methylmaleimide (560 mg, 5 mmol) in MeCN (50ml) was boiled under reflux for 12 h. The solvent was removed under reduced pressure to give the product (25b) as a brown solid (1.21g, 67%), which crystallised from ethanol as yellow plates m.p. 247-249°C (Found: C, 66.55; H, 4.3; N, 11.4. $C_{20}H_{15}N_3O_4$ requires C, 66.45; H, 4.2; N, 11.65%); ν_{max} 3280, 1690, 1590, 1280 and 720 cm^{-1}; m/z(%) 361(M^+, 48), 285(21), 284(100), 228(23), 107(38) and 77(10); δ ($CDCl_3$, CF_3CO_2D) 2.96(s, 3H, NMe), 3.69(d, 1H, 6a′-H, J 7.92Hz), 3.98(t, 1H, 3a′-H, J 7.81Hz), 5.82(d, 1H, 3′-H, J 7.67Hz), 7.98-8.11(m, 5H, ArH), 8.64(d, 1H, pyridine γ-H, J 8.91Hz), 8.84(d, 1H, pyridine α-H, J 5.42Hz) and 9.14(s, 1H, pyridine α-H); ^{1}H NOESDY (%): irradiation of 6a′-H caused enhancements of 3a′-H (6) and ArH(6); irradiation of 3a′-H caused enhancements of 6a′-H (10) and 3′-H(6); irradiation of 3′-H caused enhancements of 3a′-H (10), py α-H (4), and py γ-H (7).

Cycloadducts from 2,2-Di(piperidino)indane-1,3-dione A solution of 2,2-di(N-piperidino) indane-1,3-dione (500 mg, 1.6 mmol) prepared according to Johnson and McCaldin's method,[22] and N-methylmaleimide (360 mg, 3.2 mmol) in dry toluene (14 ml) was boiled under reflux for 3 h. Work up in the usual way gave a yellow solid (670 mg, 90%) whose p.m.r. spectrum showed it to comprise a 1:1 mixture of Michael adduct and cycloadducts [1:2 mixture of endo-(28)- and exo-(29)-isomers]; an unidentified compound was also present in trace amount. Separation of the products was achieved by flash chromatography using petroleum ether and ether (1:1) as solvent.

(28) Yellow prisms from ether-methanol contaminated with some of the exo-isomer (29). δ 8.0(m, 4H, ArH), 3.7(m, 1H, 3b-H), 3.5(t, 1H, 3a-H, J 8Hz), 3.3(d, 1H, 9a-H, J 8Hz), 3.0(s, 3H, NMe), 2.6(m, 1H, 7-H), 2.4(m, 1H, 7-H), 2.2(m, 1H, 4-H), 1.8(m, 1H, 4-H), 1.5(m, 3H, 5-H, 6-H_2) and 1.3(m, 1H, 5-H); ^{1}H NOEDSY (%): irradiation of 3a-H caused enhancement of 9a-H(11) and 3b-H(5); irradiation of 3b-H caused enhancement of 3a-H(8).

(29) Yellow rods (from ether/petroleum ether), m.p. 203-205°C (Found: C, 67.6; H, 5.35; N, 8.2. $C_{19}H_{18}N_2O_4$ requires C, 67.45; H, 5.35; N, 8.3%); m/z (%) 338(M^+, 100), 337(5), 321(5), 281(20) and 148(13); δ 8.0 (t, d, 4H, ArH), 3.7(d, 1H, 9a-H, J 9Hz), 3.4(m, 1H, 3b-H), 3.2(t, 1H, 3a-H, J 8.8Hz), 3.0(s, 3H, NCH_3), 3.5(m, 1H, 7-H), 3.3(m, 2H, 4-H and 7-H), 2.8(m, 1H, 4-H), 2.5(m, 3H, 5-H and 6-CH_2) and 2.3(m, 1H, 5-H); ^{1}H NOEDSY (%): irradiation of 3b-H caused enhancement of 4-H (7); irradiation of 9a-H caused enhancement of 3a-H (9); irradiation of 3a-H caused enhancement of 9a-H (17).

Acenaphthenequinone Cycloadducts



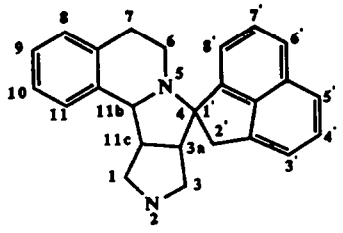
1,1′,2,3′,3a′,4′,6′,6a′-Octahydro spiro[acenaphthyleno-2,1′-pyrrolo[3,4-c]pyrrole skeleton.

1,1′,2,3′α,3a′,4′,6′,6a′α-Octahydro-3′-(4-methoxyphenyl)-5′-methylspiro[acenaphthenyl-2,1′-pyrrolo(3,4-c)pyrrole]-1,4′,6′-trione(31a). A solution of acenaphthenequinone (760 mg, 5 mmol), 4-methoxybenzylamine (690 mg, 5 mmol) and N-methylmaleimide (560 mg, 5 mmol) in MeCN (50ml) was boiled under reflux for 24 h. The solvent was removed under reduced pressure, and the resulting gum triturated with ether to give the product as a brown solid (1.40g, 68%), which crystallised from methanol as colourless prisms m.p. 262-264°C (Found: C, 72.8; H, 4.9; N, 6.85. $C_{25}H_{20}N_2O_4$ requires C, 72.8; H, 4.9; N, 6.8%); ν_{max} 3340, 2900, 1700, 1600, 1505 and 780 cm^{-1}; m/z(%) 412(M^+, 100), 411(26), 354(28), 326(21), 304(77), 301(21) and 161(20); δ 2.52(s, 1H, NH), 3.01(s, 3H, NMe), 3.43(d, 1H, 6a′-H, J 7.76Hz), 3.81(s, 3H, OMe), 3.87(t, 1H, 3a′-H, J 8.22Hz), 5.65(d, 1H, 3′-H, J 8.54Hz), 6.89(m, 2H, ArH), 7.36(m, 2H, ArH) and 7.51-8.16(m, 6H, ArH); ^{1}H NOESDY (%): irradiation of 6a′-H caused enhancement of 3a′-H (13); irradiation of 3a′-H caused enhancements of 6a′-H (13) and 3′-H (16); irradiation of 3′-H caused enhancements of 3a′-H (17) and ArH (14).

1,1′,2,3′α,3a′,4′,6′,6a′α-Octahydro-3′-(3-pyridyl)-5′-methylspiro[acenaphthenyl-2,1′-pyrrolo[3,4-c]pyrrole]-1,4′,6′-trione(31b) (with D. Henderson). Prepared in analogous manner to that described above from acenaphthenequinone (910 mg), 3-aminomethylpyridine (540 mg) and N-methylmaleimide (560 mg) in acetonitrile (50 ml). After 6 h boiling under reflux, work up afforded the product (1.2 g, 63%) as yellow plates from acetonitrile, m.p. 244-246°C (Found: C, 71.95; H, 4.5; N, 10.9. $C_{23}H_{17}N_3O_3$ requires C, 72.05; H, 4.45; N, 10.95%); ν_{max} 3442, 2920, 1696, 1429, 1283, 1091, 794 and 777 cm^{-1}; m/z(%) 383(M^+, 100), 298(10), 272(10), 243(12), 165(12) and 149(10); δ 2.62(d, 1H, NH), 2.99(s, 3H, NMe), 3.45(d, 1H, 6a′-H, J 7.8Hz), 3.88(t, 1H, 3a′-H), 5.69(dd, 1H, 3′-H) and 7.26-8.67(m, 10H, ArH); ^{1}H NOEDSY (%): irradiation of 3a′-H caused enhancement of 3′-H(10) and 6a′-H(11).

Cycloadducts and Michael adduct from the reaction of acenaphthenequinone, 1,2,3,4-tetrahydroisoquinoline and N-methylmaleimide. A solution of acenaphthenequinone (550 mg, 3 mmol) and 1,2,3,4-tetrahydroisquinoline (400 mg, 3 mmol) in dry toluene (14 ml) was boiled under reflux for 40 mins using a Dean-Stark trap. N-Methylmaleimide (330 mg, 3 mmol) was then added and boiling continued for a further two hours. Work up in the usual way gave a mixture of cycloadducts (670 mg, 55%, exo: endo, 1:1) and Michael adduct (230 mg, 32%) which were separated by flash chromatography eluting with

3:2 v/v petroleum ether/ether.



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

(34) Endo-isomer. Yellow prisms from ether-petroleum ether, m.p. 248-250°C (Found: C, 76.55; H, 5.1; N, 6.95. $C_{26}H_{20}N_2O_3$ requires C, 76.45; H, 4.9; N, 6.85%); m/z (%) 408(M^+, 100), 380(7), 379(22), 350(16), 322(9), 297(11), 296(13), 295(7), 294(15), 282(41), 241(27), 182(17), 154(30) and 126 (44); δ 8.1(d, 1H, ArH), 7.9(q, 2H, ArH), 7.8 and 7.7(2 x t, 2 x 1H, ArH), 7.5(d, 1H, ArH), 7.2(m, 3H, ArH), 7.0(d, 1H, ArH), 5.5(d, 1H, 11b-H), 4.0(t, 1H, 11c-H), 3.6(d, 1H, 3a-H), 3.0(s, 3H, NMe), 2.6(m, 2H, 6-CH_2) and 2.4(m, 2H, 7-CH_2); ^{1}H NOEDSY(%): irradiation of 11c-H caused enhancement of 3a-H(17) and 11b-H(7); irradiation of 11b-H caused enhancement of 11c-H(12) and 3a-H(4).

(35) Exo-isomer. Yellow prisms from methanol, contaminated with traces of the endo-isomer. δ 8.3-7.5(m, 7H, ArH), 7.2(m, 2H, ArH), 7.0(d, 1H, ArH), 5.0(d, 1H, 11b-H), 4.0(d, 1H, 3a-H), 3.7(t, 1H, 11c-H), 3.0(s, 3H, NMe), 2.9(m, 1H, 6-H), 2.7-2.6(m, 2H, 6-H, 7-H) and 2.4(m, 1H, 7-H); ^{1}H NOEDSY (%): irradiation of 11c-H caused enhancement of 3a-H(11) and 11b-H(3).

2-[3′-(2′,5′-Dioxo-1′-methylpyrrolidinyl)]-1,2,3,4 -tetrahydroisoquinoline(33). Colourless rods (chloroform-petroleum ether) m.p. 135-136°C (Found: C, 68.6; H, 6.6; N, 11.6. $C_{14}H_{16}N_2O_2$ requires C, 68.85; H, 6.6; N, 11.45%); ν_{max} 1770, 1690, 1440, 800, 755, 710 and 675 cm^{-1}; m/z(%) 244(M^+, 2), 243(5), 133(11), and 132(100); δ 2.70-3.03(m, 6H, 1-, 3- and 4-H), 3.04(s, 3H, NMe), 3.76(d, 1H, 4′-H, J 14.37Hz), 4.01(q, 1H, 3′-H, J 5.01Hz), 4.08(d, 1H, 4′-H, J 14.45Hz) and 7.01-7.27(m, 4H, ArH).

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