X=Y–ZH Systems as Potential 1,3-Dipoles. Part 9.[1] Aza-allyl Anion Precursors from the Reaction of (1,3-Dioxoindan-2-ylidene)malononitrile with α-Amino Acids and their Methyl Esters

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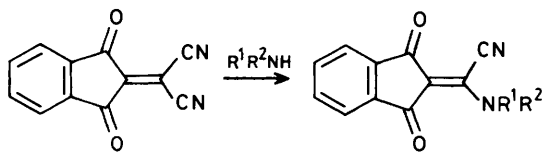
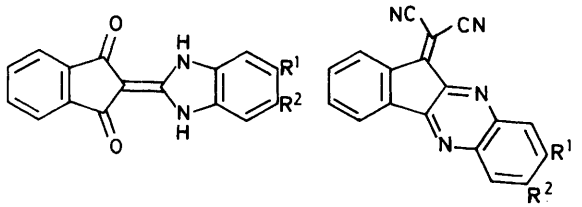
Glycine, valine, and α-amino acid esters react with (1,3-dioxoindan-2-ylidene)malononitrile (**1**) by a Michael addition–elimination mechanism with replacement of one cyano group by the α-amino acid or α-amino acid ester entity. These adducts undergo a triethylamine-catalysed stereospecific cycloaddition to *N*-methylmaleimide at room temperature with loss of the remaining cyano group in >70% yield. The cycloaddition is believed to be a [3 + 2] anionic cycloaddition involving a hydrogen-bonded aza-allyl anion.

Junek and co-workers have shown that (1,3-dioxoindan-2-ylidene)malononitrile (**1**) reacts with alkylamines, arylamines, and hydrazines by a Michael addition–elimination mechanism with loss of one cyano group to give the corresponding mono-



(**1**) (**2**)a; R^1 = R^2 = alkyl; b; R^1 = H, R^2 = aryl; c; R^1 = H, R^2 = NMe_2

amino derivatives (**2a**—**c**).[2] 1,2-Diaminoaryl compounds similarly effect elimination of both cyano groups with formation of compounds (**3**) and (**4**).[3] Simple MO calculations showed



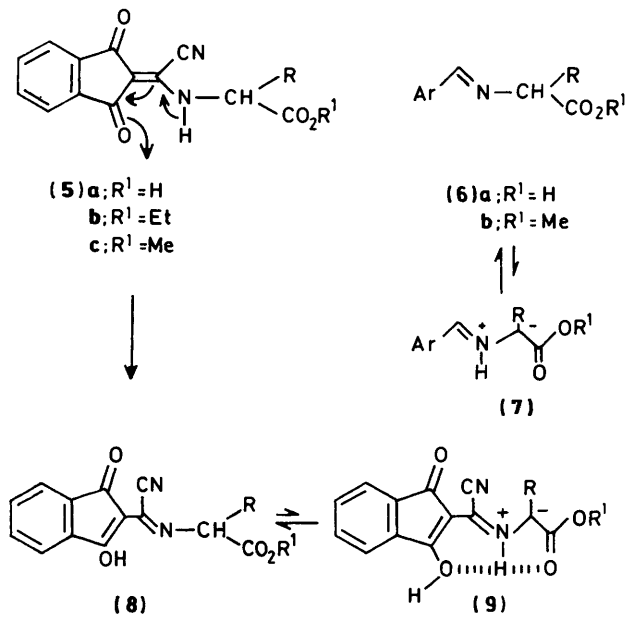
(**3**) (**4**)

that the Michael addition–elimination sequence was preferred over attack at the carbonyl groups leading to imine formation.[4]

The reactions of the malononitrile (**1**) with α-amino acids or their esters have not been reported and we thought that the expected products (**5**) of such reactions might function as precursors of azomethine ylides. Thus, we have shown in extensive studies[5] that imines of α-amino acids[1] and their esters[6] undergo thermal equilibration with the corresponding azomethine ylides by a formal 1,2-H shift [(**6**) ⇌ (**7**)]. Azomethine ylide (**7**) formation is stereospecific and kinetically controlled.[6]

For the malononitrile (**5**), azomethine ylide formation might occur in a number of ways including a 1,5-H shift (**5**, arrows) generating compound (**8**) followed by prototropy [(**8**) ⇌ (**9**)]. The potential for 1,5-H shifts has proved a valuable concept in identifying other substrates as potential 1,3-dipoles in both oximes[7] and iminium species,[8] although precise mechanistic details of these processes remain to be elucidated.

Glycine reacted rapidly (10 min) with the malononitrile (**1**) in aqueous ethanol at 50 °C to give compound (**5a**; R = H) in



(**5**)a; R^1 = H; b; R^1 = Et; c; R^1 = Me

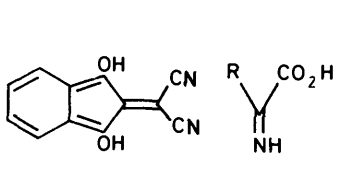
(**6**)a; R^1 = H; b; R^1 = Me

(**7**)

(**8**) (**9**)

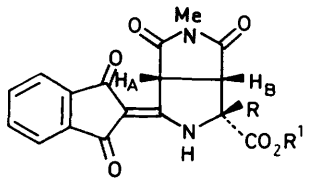
42% yield. Most other α-amino acids (alanine, phenylalanine, tryptophan, leucine, and isoleucine) reacted with compound (**1**) in aqueous acetonitrile at 50 °C to give (1,3-dihydroxy-2*H*-inden-2-ylidene)malononitrile (**10**),[9] but none of the corresponding Michael addition–elimination product (**5a**) was detected except for valine which gave a low (14%) yield of compound (**5a**; R = Pr^i) in addition to compound (**10**). The formation of the reduction product (**10**) suggests that the amino acids are being oxidised to the corresponding imino acids (**11**). However, no attempt was made to investigate the fate of the α-amino acids in these latter cases. In contrast to the α-amino acids, the corresponding esters react with the malononitrile (**1**) in acetonitrile at room temperature to give the expected adducts (**5b**; R = H) and (**5c**; R = Me, Pr^i, Ph, CH_2CO_2Me) in 53—68% yield as yellow crystalline solids.

The amino acid adduct (**5a**; R = H) reacts with *N*-methylmaleimide in aqueous dimethylformamide at 100 °C over 30 min to give the cycloadduct (**12a**; R = H) in 71% yield. The α-amino acid ester derivatives (**5b**; R = H) and (**5c**; R = Me



(10)

(11)

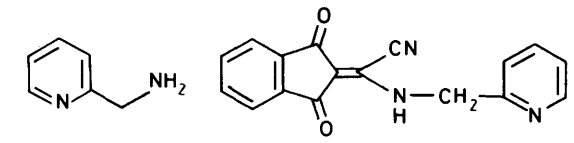


(12)a; R^1=H
b; R^1=Et
c; R^1=Me

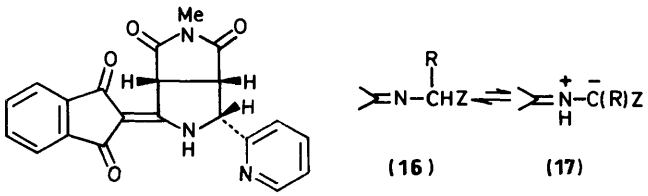
or Ph) react with *N*-methylmaleimide in acetonitrile at room temperature over 1 h in the presence of 1 mol equiv. of triethylamine to give the corresponding cycloadducts (**12b**; R = H) and (**12c**; R = Me, Ph) in >70% yield whilst compound (**5c**; R = Pr^i or CH_2CO_2Me) failed to react even in boiling acetonitrile. In the absence of triethylamine, the cycloaddition is slow and incomplete after 16 h at room temperature. The aminomethylpyridine (**13**) reacts with the malononitrile (**1**) to give compound (**14**). Alternatively the reaction of compounds (**13**), (**1**), and *N*-methylmaleimide in acetonitrile at room temperature in the presence of 1 mol equiv. of triethylamine gives the corresponding cycloadduct (**15**) directly. We have previously identified a range of groups Z, including the 2-pyridyl entity, that activate α-methine protons in imines (**16**) sufficiently to promote ylide formation (**17**).[10]

The stereochemistry of the cycloadducts (**12a**—**c**) and (**15**) was established by n.O.e. difference spectroscopy. A typical set of values is provided by (**12a**; R = H_C) in which irradiation of H_B effects enhancement of the signals of both H_A (16.5%) and H_C (12.5%).

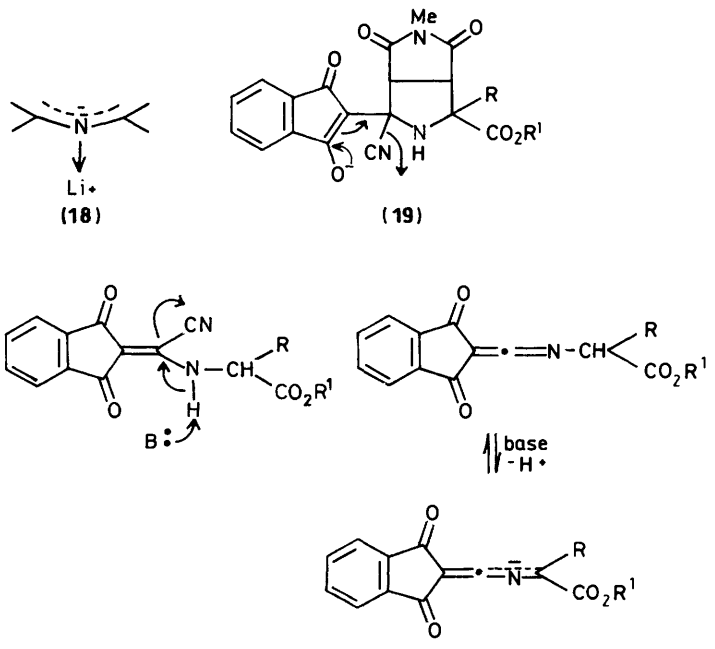
The precise nature of the 4π-component in the cycloadditions leading to compounds (**12a**—**c**) and (**15**) is not clearly defined although the efficacy of triethylamine in promoting the cycloaddition suggests the reaction probably involves a [3 + 2] anionic cycloaddition rather than the azomethine ylide (**9**). Anionic cycloadditions involving aza-allyl anions were first reported by Kauffmann *et al.*,[11] although there is a distinct possibility that these reactions involve the lithiated anion (**18**)



(13) (14)



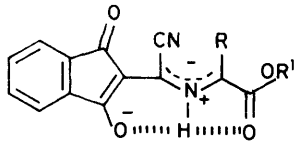
(15) (16) (17)



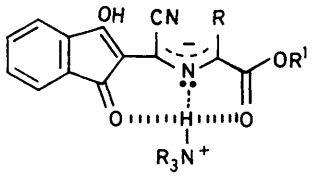
(18) (19) (20)

Scheme.

and are examples of metallo-1,3-dipoles.[12,13] Another problem is that the remaining cyano group in the malononitrile (**5**) could be lost subsequent to (**19**; arrows), or prior to (Scheme), cycloaddition. Other possible reactive intermediates include compound (**20**) (Scheme), the anion (**21**), and the triethylammonium hydrogen-bonded species (**22**). We have recently described anionic 4π-sulphinyl aminomethamide species related to compound (**20**).[14] It is clear from the stereochemistry of the cycloadducts that the reactive 4π-species must have a configuration analogous to compound (**21**) or (**22**). Bifurcated and trifurcated hydrogen bonding of the type suggested in compounds (**21**) and (**22**) are well known[15] and we have previously



(**21**)



(**22**)

suggested that hydrogen bonding is an important feature in the stereospecific, kinetically controlled, formation of azomethine ylides from imines of α-amino acid esters.[6] On balance, we favour anionic cycloaddition *via* compound (**21**) or (**22**) with loss of cyanide subsequent to cycloaddition for these processes.

Experimental

General spectroscopic details were as previously noted.[16] (1,3-Dioxoindan-2-ylidene)malononitrile (**1**) was prepared according to the literature procedure.[17]

Reaction of (1,3-*Dioxoindan*-2-*ylidene*)*malononitrile* (**1**) *with* α-*Amino Acids.*—*Glycine.* Glycine (36 mg, 4.8 mmol) in water (10 ml) was added to a solution of (1,3-dioxoindan-2-ylidene)-malononitrile (1 g, 4.8 mmol) in ethanol (40 ml) at 50 °C. The mixture was stirred at 50 °C for 10 min and then allowed to cool to room temperature when the *product* (**5a**; R = H) crystallised as yellow plates (540 mg, 44%), m.p. 187—189 °C (Found: C, 59.15; H, 3.25; N, 10.9. $C_{13}H_8N_2O_4 \cdot 0.5H_2O$ requires C, 58.85; H, 3.4; N, 10.55%); *m*/*z* (%) 256 (M^+, 13), 212 (100), 185 (44), and 44 (46); $\nu_{max.}$ 3 230, 2 210, 1 715, 1 695, and 1 650 cm^{-1}; δ[$CDCl_3$ + $(CD_3)_2SO$] 7.77 (4 H, s, ArH) and 4.37 (2 H, s, CH_2).

Valine. Valine (560 mg, 4.8 mmol) in water (20 ml) was added to a solution of (1,3-dioxoindan-2-ylidene)malononitrile (1 g, 4.8 mmol) in acetonitrile (40 ml). The mixture was stirred at 50 °C for 20 min during which time the by-product (1,3-dihydroxy-2*H*-indene-2-ylidene)malononitrile (300 mg, 30%), m.p. > 250 °C[9] precipitated and was filtered off. Concentration of the filtrate afforded the *product* (**5a**; R = Pr^i) as yellow needles (200 mg, 14%), m.p. 165—166 °C (Found: C, 64.2; H, 4.8; N, 9.65. $C_{16}H_{14}N_2O_4$ requires C, 64.4; H, 4.75; N, 9.4%); *m*/*z* (%) 298 (M^+, 27), 283 (34), 254 (45), 211 (75), and 44 (100); $\nu_{max.}$ 3 200, 2 210, 1 725, 1 690, and 1 640 cm^{-1}; δ[$CDCl_3$ + $(CD_3)_2SO$] 10.16 (1 H, s, NH), 7.85 (4 H, m, ArH), 4.42 (1 H, br s, CHN), 2.50 (1 H, m, CH), and 1.07 (6 H, t, 2 × Me).

Reaction of (1,3-*Dioxoindan*-2-*ylidene*)*malononitrile* (**1**) *with* α-*Amino Acid Esters.*—*Ethyl glycinate.* Glycine ethyl ester hydrochloride (670 mg, 4.8 mmol) and (1,3-dioxoindan-2-ylidene)malononitrile (1 g, 4.8 mmol) were suspended in 20% (v/v) aqueous acetonitrile (25 ml). Triethylamine (0.7 ml, 5 mmol) was added and the mixture stirred at room temperature for 20 min. The solvent was then evaporated and the residue crystallised from methylene dichloride–ethanol to afford the *product* (**5b**; R = H) as yellow needles (720 mg, 53%), m.p. 135—136 °C (Found: C, 63.45; H, 4.4; N, 10.05. $C_{15}H_{12}N_2O_4$ requires C, 63.35; H, 4.25; N, 9.85%); *m*/*z* (%) 284 (M^+, 52), 211 (100), and 184 (44); $\nu_{max.}$ 3 240, 2 240, 1 725, 1 700, and 1 650 cm^{-1}; δ 9.87 (1 H, s, NH), 7.77 (4 H, m, ArH), 4.43 (2 H, d, CH_2), 4.31 (2 H, q, CH_2O), and 1.33 (3 H, t, $MeCH_2$).

Methyl alaninate. Reacted in a similar manner to that described above using alanine methyl ester hydrochloride. The *product* (**5c**; R = Me) (67%) crystallised from methylene dichloride–methanol as yellow needles, m.p. 166—167 °C (Found: C, 63.2; H, 4.1; N, 9.85. $C_{15}H_{12}N_2O_4$ requires C, 63.35; H, 4.25; N, 9.85%); *m*/*z* (%) 284 (M^+, 23), 225 (100), and 198 (67); $\nu_{max.}$ 3 260, 2 240, 1 740, 1 705, and 1 660 cm^{-1}; δ 9.95 (1 H, d, NH), 7.77 (4 H, m, ArH), 4.67 (1 H, m, C*H*Me), 3.86 (3 H, s, MeO), and 1.70 (3 H, d, CH*Me*).

Methyl valinate. Reacted in a similar manner to that described above using valine methyl ester hydrochloride. The *product* (**5c**; R = Pr^i) (65%) crystallised from aqueous methanol as yellow needles, m.p. 98—99 °C (Found: C, 65.2; H, 4.95; N, 9.05. $C_{17}H_{16}N_2O_4$ requires C, 65.35; H, 5.15; N, 8.95%); *m*/*z* (%) 312 (M^+, 21), 253 (100), and 226 (20); $\nu_{max.}$ 3 240, 2 200, 1 730, 1 700, and 1 655 cm^{-1}; δ 10.11 (1 H, d, NH), 7.77 (4 H, m, ArH), 4.51 (1 H, dd, CHN), 3.86 (3 H, s, MeO), 2.45 (1 H, m, CH), and 1.10 (6 H, m, 2 × Me).

Methyl phenylglycinate. Reacted in a manner analogous to that described above. The *product* (**5c**; R = Ph) (65%) crystallised from methylene dichloride–methanol as yellow needles, m.p. 160—161 °C (Found: C, 69.55; H, 4.05; N, 8.1. $C_{20}H_{14}N_2O_4$ requires C, 69.35; H, 4.05; N, 8.1%); *m*/*z* (%) 346 (M^+, 4), 287 (100), and 260 (26); $\nu_{max.}$ 3 190, 2 240, 1 730, 1 705, and 1 660 cm^{-1}; δ 10.56 (1 H, d, NH), 7.75 (4 H, m, ArH), 7.44 (5 H, m, ArH), 5.60 (1 H, d, CHN), and 3.86 (3 H, s, MeO).

Dimethyl aspartate. Reacted in a similar manner to that described above. The *product* (**5c**; R = CH_2CO_2Me) (68%) crystallised from methylene dichloride–methanol as yellow needles, m.p. 157—158 °C (Found: C, 59.65; H, 4.1; N, 8.3. $C_{17}H_{14}N_2O_6$ requires C, 59.65; H, 4.1; N, 8.2;%); *m*/*z* (%) 342 (M^+, 38), 283 (41), and 251 (100); $\nu_{max.}$ 3 180, 2 230, 1 735, 1 705, and 1 655 cm^{-1}; δ 10.32 (1 H, d, NH), 7.76 (4 H, m, ArH), 4.90 (1 H, m, CHN), 3.80 and 3.85 (2 × 3 H, 2 × s, 2 × MeO), and 3.29 and 3.07 (2 H, 2 × dd, CH_2CH).

2-*Aminomethylpyridine.* (1,3-Dioxoindan-2-ylidene)malononitrile (500 mg, 2.4 mmol) and 2-aminomethylpyridine (0.25 ml, 2.4 mmol) were dissolved in acetonitrile (20 ml) and the resulting mixture was stirred at room temperature for 1 h during which time the *product* (**14**) (420 mg, 61%) crystallised as yellow plates, m.p. 177—179 °C (Found: C, 70.6; H, 3.9; N, 14.35. $C_{17}H_{11}N_3O_2$ requires C, 70.6; H, 3.85; N, 14.55%); *m*/*z* (%) 298 (M^+, 100), 262 (M − HCN, 41), 144 (24), and 107 (36); $\nu_{max.}$ 2 240, 1 695, and 1 655 cm^{-1}; δ[$(CD_3)_2SO$] 10.6 (1 H, s, NH), 8.6 (1 H, d, PyH), 7.85 (1 H, d, PyH), 7.78 (4 H, s, ArH), 7.45 (1 H, d, PyH), 7.36 (1 H, t, PyH), and 4.99 (2 H, s, CH_2).

Cycloadditions.—4-(1,3-*Dioxoindan*-2-*ylidene*)-7-*methyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylic acid* (**12a**; R = H). A mixture of the glycine derivative (**5a**; R = H) (256 mg, 1 mmol) and *N*-methylmaleimide (111 mg, 1 mmol) in 20% aqueous dimethylformamide (10 ml) was heated at 100 °C for 30 min. After addition of a little water the mixture was set aside to cool and crystallise. The product (470 mg, 71%) separated as colourless plates, m.p. > 250 °C (Found: C, 56.75; H, 4.0; N, 7.8. $C_{17}H_{12}N_2O_6 \cdot H_2O$ requires C, 57.0; H, 3.95; N, 7.8%); *m*/*z* (%) 296 ($M^+ - CO_2$, 15); $\nu_{max.}$ 3 280, 1 720, 1 695, and 1 640 cm^{-1}; δ[$CDCl_3$ + $(CD_3)_2SO$] 10.00 (1 H br s, NH), 7.73 (4 H, m, ArH), 5.31 (1 H, d, H_A), 4.76 (1 H, d, H_C), 4.03 (1 H, dd, H_B), and 2.79 (3 H, s, NMe).

Ethyl 4-(1,3-*dioxoindan*-2-*ylidene*)-7-*methyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylate* (**12b**; R = H). A solution of the ethyl glycinate derivative (**5b**; R = H) (284 mg, 1 mmol) and *N*-methylmaleimide (111 mg, 1 mmol) was dissolved in acetonitrile (20 ml) and triethylamine (0.14 ml, 1 mmol) added. After the mixture had been stirred for 5 min at room temperature, the cycloadduct crystallised out and was filtered off to give the *product* (280 mg, 76%) as colourless plates, m.p. >250 °C (Found: C, 62.1; H, 4.5; N, 7.6. $C_{19}H_{16}N_2O_6$ requires C, 61.95; H, 4.4; N, 7.6%); *m*/*z* (%) 368 (M^+, 32), 295 (62), and 238 (100); $\nu_{max.}$ 3 240, 1 740, 1 700, and 1 640 cm^{-1}; δ[$CDCl_3$ + $(CD_3)_2SO$] 9.8 (1 H, s, NH), 7.67 (4 H, m, ArH), 5.32 (1 H, d, H_A), 4.87 (1 H, d, H_C), 4.09 (3 H, m, H_B and CH_2O), 2.83 (3 H, s, NMe), and 1.23 (3 H, t, $MeCH_2$). Irradiation of the signal for H_A effected an enhancement in the signal for H_B (12%) and irradiation of H_C also caused enhancement of H_B (15.5%).

Methyl 4-(1,3-*dioxoindan*-2-*ylidene*)-2,7-*dimethyl*-6,8-*dioxo*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylate* (**12c**; R = Me). Prepared from the methyl alaninate derivative (**5c**; R = Me) in an analogous manner to that described above but with a reaction time of 1 h. The *product* (76%) crystallised as yellow plates, m.p. >250 °C (Found: C, 62.15; H, 4.35; N, 7.4. $C_{19}H_{16}N_2O_6$ requires C, 61.95; H, 4.4; N, 7.6%); *m*/*z* (%) 368 (M^+, 14), 309 (83), and 252 (100); $\nu_{max.}$ 3 280, 1 745, 1 715, and 1 645 cm^{-1}; δ[$(CD_3)_2SO$] 10.2 (1 H, s, NH), 7.69 (4 H, s, ArH), 5.40 and 3.27 (2 × 1 H, 2 × d, H_A and H_B), 3.25 (3 H, s, MeO), 2.80 (3 H, s, NMe), and 1.70 (3 H, s, Me). Irradiation of the 2-Me signal effected enhancement of the signal for H_B (11%) and irradiation of H_A also caused enhancement of H_B (7.5%).

Methyl 4-(1,3-*dioxoindan*-2-*ylidene*)-7-*methyl*-6,8-*dioxo*-2-*phenyl*-3,7-*diazabicyclo*[3.3.0]*octane*-2-*carboxylate* (**12c**; R = Ph). Prepared (75%) from the methyl phenylglycinate derivative (**5c**; R = Ph) in a similar manner to that described above but with a 1 h reaction time. The *product* crystallised as colourless plates, m.p. >250 °C (Found: C, 67.2; H, 4.45; N, 6.55. $C_{24}H_{18}N_2O_6$ requires C, 67.0; H, 4.2; N, 6.5%); *m*/*z* (% 430 (M^+, 3), 371 (100), and 314 (69); $\nu_{max.}$ 3 220, 1 750, 1 710, and 1 650 cm^{-1}; δ[$(CD_3)_2SO$] 10.84 (1 H, s, NH), 7.75 (4 H, s, ArH), 7.47 (5 H, m, ArH), 5.42 (1 H, d, H_A), 4.00 (1 H, d, H_B) 3.57 (3 H, s, MeO), and 2.92 (3 H, s, NMe). Irradiation of the signal for H_B caused enhancement of the signals for H_A (17%) and the *o*-phenyl protons (11%).

4-(1,3-*Dioxoindan*-2-*ylidene*)-7-*methyl*-6,8-*dioxo*-2-*pyridyl*-3,7-*diazabicyclo*[3.3.0]*octane* (**15**). 2-Aminomethylpyridine (530 mg, 4.8 mmol) was added to a solution of (1,3-dioxoindan-2-ylidene)malononitrile (1 g, 4.8 mmol) and *N*-methylmaleimide (532 mg, 4.8 mmol) in acetonitrile (30 ml). Triethylamine (0.7 ml, 5 mmol) was then added and the mixture stirred at room temperature for 1 h during which time the *cycloadduct* (1.26 g, 70%) crystallised as yellow plates, m.p. >250 °C (Found: C, 67.75; H, 4.2; N, 11.1. $C_{21}H_{15}N_3O_4$ requires C, 67.55; H, 4.05; N, 11.25%); *m*/*z* (%) 373 (M^+, 92), 262 (100), and 228 (69); $\nu_{max.}$ 3 250, 1 780, 1 700, and 1 635 cm^{-1}; δ[$(CD_3)_2SO$] 9.88 (1 H, s, NH), 8.05 (1 H, d, PyH), 7.43 (1 H, m, PyH), 7.33 (4 H, m, ArH), 7.06 (1 H, d, PyH), 6.95 (1 H, m, PyH), 5.18 (1 H, d, H_A), 5.05 (1 H, d, H_C), 3.80 (1 H, dd, H_B), and 3.07 (3 H, s, NMe). Irradiation of the signal for H_B effected enhancements in the signals for H_A (17%) and H_C (27.5%).

Acknowledgements

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