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# 7-AZASTEROID ANALOGUES—I

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**Abstract**—Although 7-methoxy- and 6,7-dimethoxy-2-methyl-4-vinyl-isocarbostyrils could not be isolated and characterised, they have been generated *in situ* and shown to undergo cyclo-addition reactions with typical dienophiles. The enol acetate of 2-methyl-4-acetylisocarbostyril has also been trapped as its adduct with maleic anhydride and with *p*-benzoquinone.

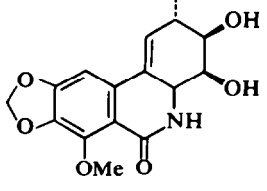
As part of a programme of work which has the synthesis of phenanthridines, benzo[c]phenanthridines, 7-azasteroids and partially reduced phenanthridines such as narciclasine (**1**), as objectives, we have been studying Diels–Alder reactions with 4-vinyl-isoquinoline derivatives. We have reported[1] that the diene ester **2a** gives the expected adducts **3a** and **4** with maleic anhydride and acrylic acid, respectively, but that the reaction with *p*-benzoquinone produces the aromatic adduct **5a**. When **2a** is treated with propiolic acid, the expected Diels–Alder adduct is not isolated; the product is **6a**. A preliminary examination of the properties of **2b** was also described,[1] when the adducts **3b** and **5b** were isolated.

In this paper we wish to report on the extension of this work to dienes that possess one or more oxygen functions in the benzenoid ring, thus providing closer analogies to the target molecules. In particular we were interested in the properties of the dienes **2c**, **2d** and **2e**; adducts derived from **2c** would provide intermediates on the route to the 7-azasteroid analogues.

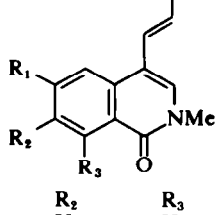
7-Methoxy-2-methylisoquinolinium iodide (**11a**) was prepared either by the classical Pomeranz–Fritsch method,[2] or by the route outlined in Scheme 1 **7a** → **10a** → **11a**. Reduction of **11a** with LAH, followed by reaction with $POCl_3$/DMF gave the vinylogous amide **13a** in 46% yield. This was oxidised with $MnO_2$ to the 4-formyliscarbostyril (**14a**), which reacted with MeMgI to give the alcohol **15a** in 75% yield. Although yields at each stage were satisfactory, the overall sequence is somewhat lengthy. An important modification became possible when it was found that the 4-hydroxy-1,2,3,4-tetrahydroisoquinoline (**9a**) could be converted directly into **13a** by reaction with the Vilsmeier reagent in an excess of $POCl_3$. Presumably the reaction proceeds via the 1,2-dihydroisoquinoline (**12a**). With an overall yield of 30% from the acetal (**7a**), the alcohol (**15a**) is now a readily available compound.

Repetition of the sequence (Scheme 1) with 3,4-dimethoxybenzaldehyde in place of *m*-methoxybenzaldehyde led to the secondary alcohol **15b** in comparable yield. However, with the isomeric 2,3-dimethoxybenzaldehyde, the synthesis broke down at **13c**, which could not be oxidised to the isocarbostyril **14c**.

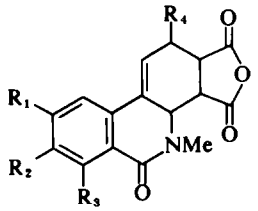
Since the isoquinoline-4-acetic acids (**16**) are readily available,[3] a shorter route to 4-vinylisoquinoline derivatives seemed possible, and this was explored (Scheme 2). The corresponding ethyl esters were, therefore, reduced with LAH to the primary alcohols (**17**), but dehydration to the 4-vinylisoquinolines (**18**) could not be achieved. Re-



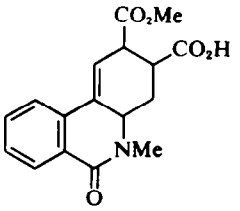
**1**



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **2a** | H | H | H | $CO_2Me$ |
| **2b** | H | H | H | H |
| **2c** | H | OMe | H | H |
| **2d** | OMe | OMe | H | H |
| **2e** | H | OMe | OMe | H |



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **3a** | H | H | H | $CO_2Me$ |
| **3b** | H | H | H | H |
| **3c** | H | OMe | H | H |
| **3d** | OMe | OMe | H | H |



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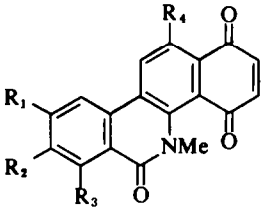
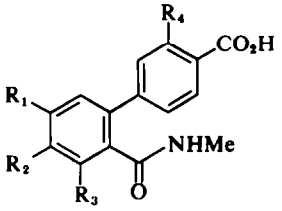


| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **5a** | H | H | H | $CO_2Me$ |
| **5b** | H | H | H | H |
| **5c** | H | OMe | H | H |
| **5d** | OMe | OMe | H | H |



| | $R_1$ | $R_2$ | $R_3$ | $R_4$ |
|---|---|---|---|---|
| **6a** | H | H | H | $CO_2Me$ |
| **6b** | H | OMe | H | H |

duction of the ester methiodide (**19a**) with LAH gave an unstable 1,2-dihydroisoquinoline (qualitative UV spectrum), but the hoped for dienamine (**20a**) could not be isolated after dehydration under acid conditions.

Attempts to dehydrate the alcohols **15a** and **15b**, to the corresponding 4-vinylisocarbostyrils (**2c** and **2d**) respectively, were not successful; the products obtained being polymeric and not readily characterised.

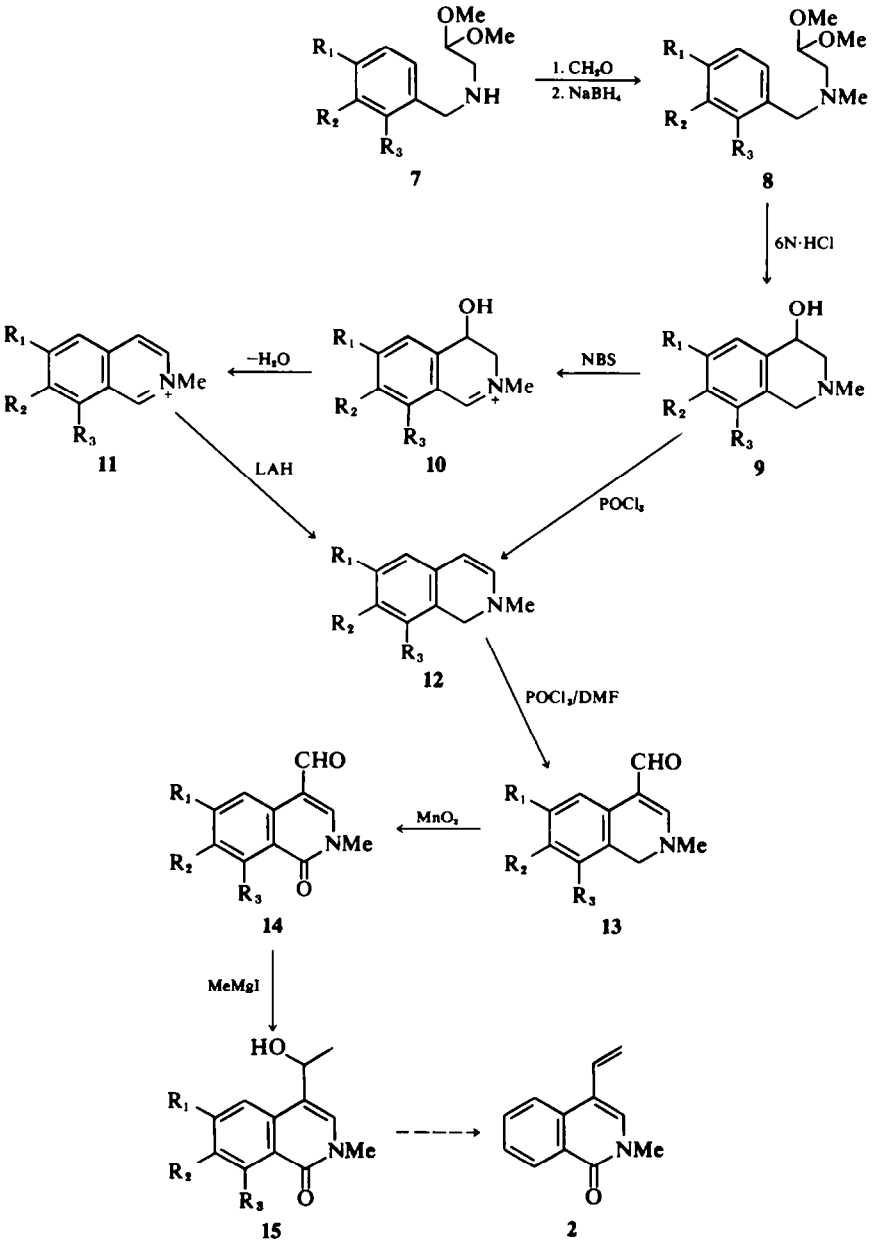
Fortunately it proved possible to carry out simultaneous dehydration and Diels–Alder additions under the conditions reported previously.[1] Thus, when a solution of **15a** and maleic anhydride in acetonitrile was heated under reflux, a 58% yield of the adduct **3c** was obtained. The structural assignment rests upon spectral evidence and analogy with the previously reported[1] work. In particular the mass spectrum exhibited an ion (the base peak) at *m/e* 215, typical for the expected retro-Diels Alder reaction. The NMR spectrum (at 100 MHz) was too complex for stereochemical assignments to be made, but the *position* of the double bond follows from the total proton count, and from the UV spectrum of the adduct.

When **15a** was heated with *p*-benzoquinone in glacial acetic acid solution, the dehydrogenated product **5c** was isolated in 72% yield. The analogous product **5d** was obtained from **15b**. When propiolic acid reacted with **15a** in refluxing acetonitrile solution, the product, obtained in good yield, proved to be the ring-opened amide **6b**, analogous to the behaviour reported[1] for the diene ester **2a**.

The electron-rich dienophiles ethyl vinyl ether and 2,5-dimethoxy-2,5-dihydrofuran failed to react with **15a** or **15b**, either in refluxing xylene or in a sealed tube at temperatures up to 200°.

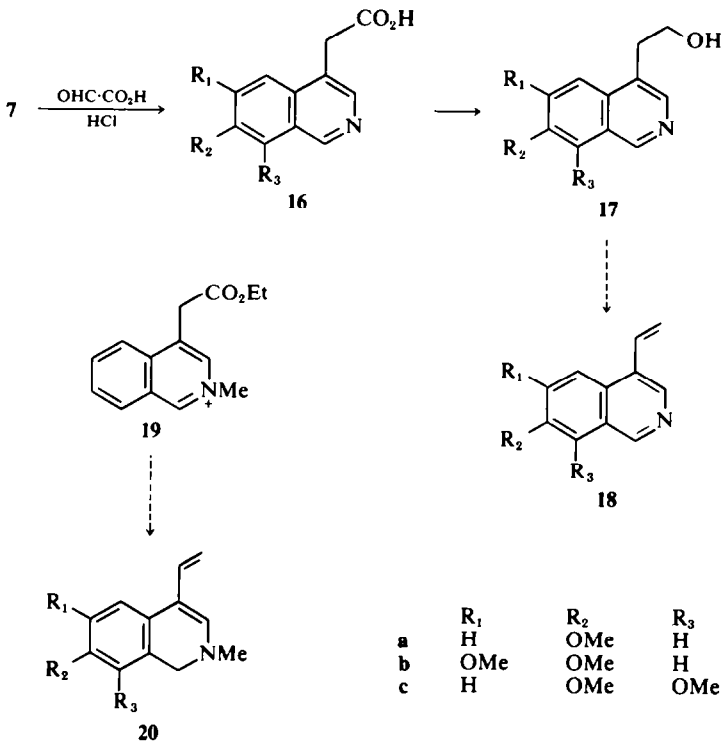
The isocarbostyril alcohols **15a** and **15b** were each oxidised to the ketoamides **21a** and **21b** respectively, but attempts to isolate the enol acetates derived from reacting these latter compounds with isopropenyl acetate were unsuccessful.

It has been shown[4] that enol acetates derived from $\alpha\beta$-unsaturated ketones need not be isolated in order that Diels Alder reactions can be carried out. This procedure has now been employed by us with the very readily available[5] 2-methyl-4-acetylisocarbostyril (**21c**), when the adduct **22** was formed. Unfortunately the product is only sparingly soluble in the solvents usually used for the measurement of NMR spectra, but structure **22** is compatible with the observed mass spectrum. The parent ion, at *m/e* 342, corresponds to an (M+1) peak, for which the authors know of no precedent and for which they cannot, at this stage, offer an explanation. The fragmentations, however, are readily understood in terms of Scheme 3. The base peak, at *m/e* 299, corresponds to ($M^+$—$CH_2$=C=O), and the retro-Diels Alder fragmentation is represented by the peak at *m/e* 243. When



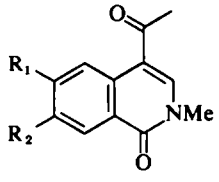

| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | H | OMe | H |
| b | OMe | OMe | H |
| c | H | OMe | OMe |

SCHEME 1




| | $R_1$ | $R_2$ | $R_3$ |
|---|---|---|---|
| a | H | OMe | H |
| b | OMe | OMe | H |
| c | H | OMe | OMe |

SCHEME 2




**21a**: $R_1 = H$; $R_2 = OMe$
**21b**: $R_1 = R_2 = OMe$
**21c**: $R_1 = R_2 = H$

the adduct **22** was treated with dilute aqueous $NaHCO_3$, the keto–amido anhydride **23** was isolated in poor yield.

When *p*-benzoquinone reacted with **21c** in the presence of isopropenyl acetate, the Diels–Alder adduct **24** precipitated out of the reaction mixture. The parent ion in the mass spectrum, at *m/e* 351, indicates that the product is the adduct **24** and not the dehydrogenation product derived from it, as had previously been found and described above. Fragment ions corresponding to the loss of keten, and to the retro Diels–Alder reaction are prominent in the spectrum. The adduct **24** is not very stable, but the dihydro derivative **25** obtained from it by reduction with zinc in acetic acid, is a stable, crystalline solid that has been fully characterised.

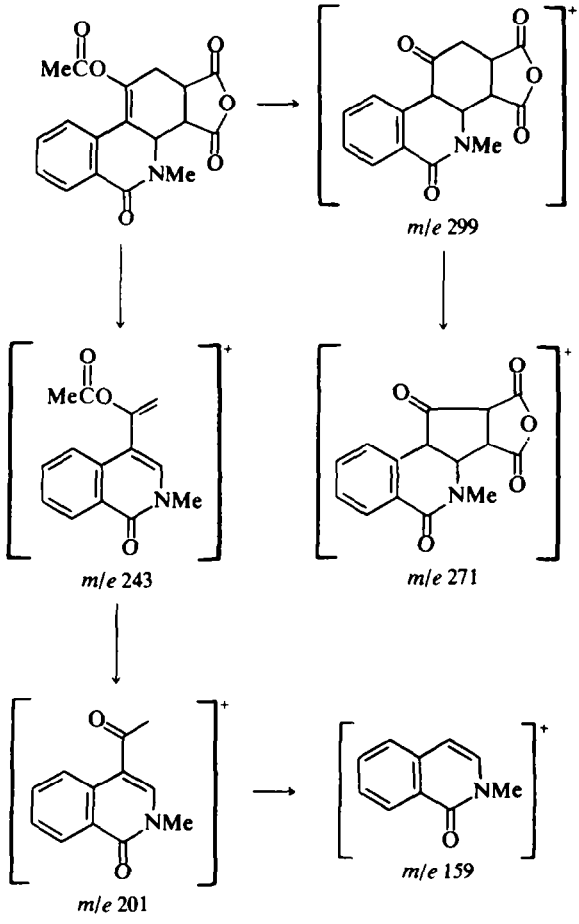
It has been reported[6] that 1,4-naphthaquinone reacts with phenylazide to give, ultimately, the anil **26**, but when attempts were made to modify **5c** in this way, starting material was recovered under all of the conditions studied.

The most useful compound to emerge from this work, as far as an intermediate for elaboration towards 7-azasteroids is concerned, is **25** and an examination of its properties is in progress.

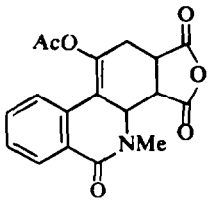
## EXPERIMENTAL

M.ps are uncorrected. UV spectra were determined on EtOH solns and IR spectra as Nujol mulls. NMR spectra were measured with a Varian A60 or HA100 spectrometer and chemical shifts are expressed as ppm downfield from TMS as internal standard. Mass spectra were recorded using A.E.I. MS12 or MS902 spectrometers.

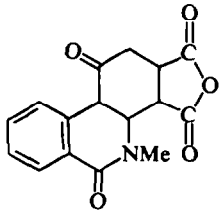
N-3-*Methoxybenzyl*-N-*methylaminoacetaldehyde dimethyl acetal* (**8a**). A soln of *m*-methoxybenzaldehyde (48g) and aminoacetal (38g) in EtOH (250 ml) was heated under reflux for 30 min then cooled. Adam's catalyst was added and the mixture was hydrogenated at atmospheric pressure and room temp. until absorption of $H_2$ had ceased. 37% HCHO (30 ml) and glacial AcOH (35 ml) was added and the mixture was hydrogenated again until no more gas was absorbed. After removal of the catalyst and evaporation under reduced pressure, the residual oil was distilled. The fraction b.p. 125–130°/0·3 mm Hg was collected (76%). The hydrochloride m.p. 145·5–146·0° was crystallised from MeOH/ether. (Found: C, 56·38; H, 7·95; N, 5·09. $C_{13}H_{22}NO_3Cl$ requires: C, 56·62; H, 7·98; N, 5·08%.)



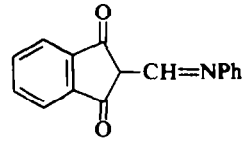

SCHEME 3



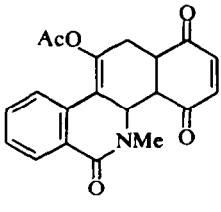

22



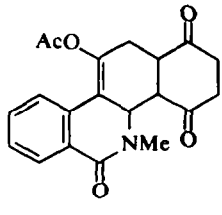

23




26




24




25

*2-Methyl-4-hydroxy-7-methoxy-3,4-dihydroisoquinolinium bromide* (**10a**). A soln of the above acetal (5 g) in 6N HCl (125 ml) was left at 25° overnight, then diluted with water, cooled and basified with 30% NaOH soln. Extraction with $CHCl_3$ gave a yellow oil of **9a**. This, without purification, was dissolved in $CHCl_3$ (60 ml) and stirred with *N*-bromosuccinimide (3·9 g) for 3 hr.[7] Filtration and evaporation of the filtrate gave the required **10a** (3·5 g; 66%), m.p. 160–162° IR: 3230, 1670, 1609, 1580 $cm^{-1}$. (Found: C, 48·48; H, 5·24; N, 5·19, $C_{11}H_{14}NO_2Br$ requires: C, 48·53; H, 5·5; N, 5·15%.)

*2-Methyl-7-methoxyisoquinolinium iodide* (**11a**). A soln of the above methobromide (3·0 g) in 6N ethanolic HCl (60 ml) was heated on a steam-bath for 60 min, then cooled and concentrated. The residue, in a small quantity

of water, was treated with solid KI. The precipitated 2-methyl-7-methoxyisoquinolinium iodide (2·7 g; 50·8%) was collected, m.p. 195–196° (lit.[2] m.p. 196–198°).

*2-Methyl-4-formyl-7-methoxy-1, 2-dihydroisoquinoline* (**13a**). A suspension of the above methiodide (5·0 g) in ether (150 ml) was treated with LAH (1·5 g). The resultant mixture was stirred at room temp for 2 hr, then excess LAH was destroyed by aqueous sodium potassium tartrate. The ether soln was decanted, dried and added to a mixture of $POCl_3$ (2·7 ml) and DMF (14·0 ml) at 0°. After heating under reflux for 2 hr, the ether was removed and crushed ice added. The mixture was made alkaline with 30% NaOH aq (*ca* 50 ml) and extracted with $CHCl_3$. A pale brown solid (1·5 g; 46%) was obtained from the $CHCl_3$ which crystallised from EtOH m.p. 138–139°. $\nu_{max}$ $cm^{-1}$ 1645, 1603; NMR ($CDCl_3$): 3·0 3H s (NMe); 3.72 3H s (OMe); 4·45 2H s ($C_1H_2$); 6·55 3H m ($C_3-H+C_6-H+C_8-H$); 8·55 1H d (J = 7Hz)($C_5-H$); 8·99 1H s (CHO). (Found: C, 70·8; H, 6·24; N, 6·92. $C_{12}H_{13}NO_2$ requires: C, 71·0; H, 6·40; N, 6·89%.)

*2-Methyl-4-formyl-6,7-dimethoxy-1,2-dihydroisoquinoline* (**13b**). $POCl_3$ (15 ml) was added to a soln of **9b**[5] (3·0 g) in $CHCl_3$ (100 ml). After standing at room temp overnight, further $POCl_3$ (5 ml) and DMF (50 ml) was added to the cooled soln, which was then heated under reflux for 90 min. The $CHCl_3$ was removed at reduced pressure and the residue treated with crushed ice, then basified by the dropwise addition of 30% NaOH aq. Extraction with $CHCl_3$ (4 × 50 ml) and usual work up left a brown solid (1·91 g; 61%) which was crystallised from EtOH, m.p. 135–137°, $\nu_{max}$ $cm^{-1}$ 1645, $\lambda_{max}$ nm ($\epsilon_{max}$) 254 (16,600); 287 (13,300); NMR ($CDCl_3$) 3·0 3H s (NMe); 3·85 6H d (2 × OMe); 4·52H s ($C_1H_2$); 6·4 1H s ($C_3-H$); 6·7 1H s ($C_8-H$); 8·3 1H s ($C_5-H$); 8·9 1H s (CHO). (Found: C, 67·2; H, 6·4; N, 6·0. $C_{13}H_{15}NO_3$ requires: C, 66.9; H, 6·5; N, 6·0%.)

*2-Methyl-4-formyl-7,8-dimethoxy-1,2-dihydroisoquinoline* (**13c**). $POCl_3$ (1·5 ml) was added to a soln of 2-methyl-4-hydroxy-7, 8-dimethoxy-1,2,3,4-tetrahydroisoquinoline[7] (0·35 g) in $CHCl_3$ (10 ml). After 16 hr at room temp, the soln was treated with a soln of $POCl_3$ (0·5 ml) in DMF (5 ml). The soln was heated under reflux for 90 min, then evaporated under reduced pressure and the residue was treated with crushed ice and 30% NaOH aq. Extraction with $CHCl_3$ and work up in the usual way gave **13c** (0·23 g; 63%) as an off-white solid which crystallised from EtOH as white prisms, m.p. 142–143°, $\nu_{max}$ $cm^{-1}$ 1630, 1611, $\lambda_{max}$ nm ($\epsilon_{max}$) 247 (14,800); 285 (12,700); NMR ($CDCl_3$) 3·05 3H s (NMe); 3·8 6H d (2 × OMe); 4·55 2H s ($C_1H_2$); 6·7 1H s ($C_3-H$); 6·75 1H d (J = 8·0 Hz) ($C_6-H$); 8·2 1H d (J = 8·0 Hz) ($C_5-H$); 8·9 1H s (CHO). *m/e* (% base peak) 233 (100); 232 (86); 231 (9); 219 (11); 218 (26); 217 (23); 216 (14); 203 (23); 194 (9); 188 (9); 175 (9); 174 (17); 151 (14). (Found: C, 67·0; H, 6·6; N, 6·1. $C_{13}H_{15}NO_3$ requires: C, 66·9; H, 6·5; N, 6·0%.)

*2-Methyl-4-formyl-7-methoxyisocarbostyril* (**14a**). (i) The vinylogous amide **13a** (1·0 g) in acetone (100 ml) was stirred at room temp for 48 hr with active $MnO_2$ (5 g). The filtrate was evaporated to leave the isocarbostyril as colourless needles, m.p. 188–189° from EtOH. (0·92 g; 85%), $\nu_{max}$ $cm^{-1}$ 1663, 1615; NMR ($CDCl_3$) 3·68 3H s (NMe); 3·90 3H s (OMe); 7·55 1H br s ($C_3-H$); 7·32 1H double d (J = 8·0 Hz and J = 3·0 Hz) ($C_6-H$); 5·78 1H d (J = 3·0 Hz) ($C_8-H$); 8·88 1H d (J = 8·0 Hz) ($C_5-H$); 9·73 1H s (CHO). (Found: C, 66·2; H, 5·0; N, 6·5. $C_{12}H_{11}NO_3$ requires: C, 66·4; H, 5·06; N, 6·45%.)

(ii) A soln of **8a** (1·0 g) in 6N HCl (30 ml) was kept at 25° for 16 hr, then it was basified with 30% NaOH aq and extracted with $CHCl_3$. The $CHCl_3$ soln was dried and evaporated to leave an oily residue which was treated with a soln of $POCl_3$ (4 ml) in $CHCl_3$ (25 ml). After 3 hr at room temp, DMF (15 ml) was added and the mixture heated under reflux for 90 min. The solvent was removed under reduced pressure, and crushed ice, followed by 30% NaOH aq were added to the residue. Extraction with $CHCl_3$ led to a brown gum which was dissolved in acetone (120 ml). After addition of active $MnO_2$, the mixture was stirred for 48 hr, filtered and evaporated to leave **14a** (33%).

*2-Methyl-4-formyl-6,7-dimethoxyisocarbostyril* (**14b**). A soln of **13b** (1·5 g) in acetone (150 ml) containing $MnO_2$ was stirred at room temp for 16 hr. Usual work up gave the required **14b** (1.19 g; 75%) as white needles from MeOH, m.p. 230–232°, $\nu_{max}$ $cm^{-1}$ 1678, 1643, $\lambda_{max}$ nm ($\epsilon_{max}$): 246 (23,600); 261 (17,000); 324 (5,400); 337 (5,200); NMR ($CDCl_3$): 3·70 3H s (NMe); 4·0 6H d (2 × OMe); 7·5 1H s ($C_3-H$); 7·7 1H s ($C_8-H$); 8·4 1H s ($C_5-H$): 9·65 1H s (CHO). (Found: C, 63·3; H, 5·3; N, 5·6. $C_{13}H_{13}NO_4$ requires: C, 63·2; H, 5·3; N, 5·6%.)

*2-Methyl-7-methoxy-4-(α-hydroxyethyl) isocarbostyril* (**15a**). MeMgI (from 0·5 g Mg) in ether (150 ml) was added to a soln of **14a** (4·5 g) in THF (100 ml). After 4 hr at room temp, 10% $NH_4Cl$ aq was added, followed by sufficient water to give clear solns. Extraction with $CHCl_3$, followed by drying and evaporation of the solvent left **15a** (3·4 g; 75%) m.p. 148–149° from acetone, $\nu_{max}$ $cm^{-1}$ 3350, 1639, 1610, 1590; NMR ($CDCl_3$) 1·58 3H d (J = 6) ($CH_3CH$<); 3·1 1H broad adsorption ($OH^-$ removed by $D_2O$); 3·34 3H s (NMe); 3·92 3H s (OMe); 5·10 1H q (J = 6) ($CH_3CH$<); 6·92 1H s ($C_3-H$); 7·1–7·9 3H m ($C_5-H+C_6-H+C_8-H$), *m/e* (% base peak) 233 (59); 219 (14); 218 (100); 217 (11); 216 (14); 215 (23); 200 (9); 190 (14); 175 (9); 174 (8). (Found: C, 66·3; H, 6·4; N, 5·7. $C_{13}H_{15}NO_3 = 233$ requires: C, 66·9; H, 6·44; N, 6·01%.)

The above alcohol (0·5 g) in xylene (100 ml) was heated under reflux with fused $KHSO_4$ (5 g) for 5 hr. After filtering, the soln was evaporated and the residue (0.3 g) triturated with MeOH to give a brown solid. This was not sufficiently stable for elemental analysis, but the mass spectrum is compatible with the compound being **2c** *m/e* (% base peak): 215 (100); 201 (5); 200 (40); 186 (3·5); 185 (2·3); 184 (2·3); 172 (5); 144 (9), metastables at 186 (215→200); 148 (200→172); 120·6 (172→144). $C_{13}H_{13}NO_2 = 215$.

*2-Methyl-6,7-dimethoxy-4-(α-hydroxyethyl) isocarbostyril* (**15**). From **14b** and MeMgI in an analogous method to the above. The alcohol **15b** was obtained in 74% yield as cream needles from MeOH, m.p. 180–182°, $\nu_{max}$ $cm^{-1}$; 3350, 1648, $\lambda_{max}$ nm ($\epsilon_{max}$): 247 (47,300); 262 (33,600); 324 (10,000); 338 (9,800); NMR ($CDCl_3$): 1·50 3H d (J = 6·0 Hz) ($CH_3CH$<); 3·25 3H s (NMe); 3·90 7H d (reducing to 6H on treatment with $D_2O$) (2 × OMe + $^-OH$); 4·95 1H q (J = 6·0 Hz) $CH_3-CH$); 6·8 1H s ($C_3-H$); 7·10 1H s ($C_5-H$); 7·65 1H s ($C_8-H$). (Found: C, 63·9; H, 6·6; N, 5·4. $C_{14}H_{17}NO_4$ requires: C, 63·9; H, 6·5; N, 5·3%).

*2-Methyl-4-acetyl-6,7-dimethoxyisocarbostyril* (**21b**). A soln of the above **15b** (0·5 gg) in acetone (150 ml) was heated under reflux with $MnO_2$ for 24 hr. The acetone filtrate was dried and evaporated to leave a residue which was crystallised from MeOH to give **21b** (0·38 g; 74%) as

white cubes m.p. 190–192°, $\nu_{max}$ cm$^{-1}$: 1665, 1645, $\lambda_{max}$ nm ($\epsilon_{max}$): 247 (25,200); 261 (17,000); NMR ($CDCl_3$) 2·50 3H s ($CH_3CO$); 3·50 3H s (NMe); 4·00 6H s (2×OMe); 7·70 1H s ($C_3-H$); 7·80 1H s ($C_8-H$); 8·00 1H s ($C_5-H$). (Found: C, 64·2; H, 6·0; N, 5·4. $C_{14}H_{15}NO_4$ requires: C, 64·4; H, 5·8; N, 5·4%.)

*Diels–Alder reactions*

(a) *Maleic anhydride.* (i) A soln of **15a** (0·5 g) and maleic anhydride (0·5 g) in acetonitrile (20 ml) was heated under reflux for 17 hr. On cooling, the white crystalline product (0·39 g; 58%) was collected m.p. 276–278°, $\nu_{max}$ cm$^{-1}$ 1850, 1775, 1642, 1608, *m/e* (% base peak) 313 (13); 216 (15); 215 (100); 200 (20), metastables at 186 (215→200); 147·6 (313→215). (Found: C, 65·19; H, 4.79; N, 4·47. $C_{17}H_{15}NO_5$ requires: C, 65·47; H, 4·77; N, 4·7%.)

(ii) In a similar manner **15b** gave the adduct **3d** m.p. 190–192° in 72% yield, $\nu_{max}$ cm$^{-1}$: 1840, 1771, 1640, $\lambda_{max}$ nm ($\epsilon_{max}$) 230 (7,300); 253 (11,600); 313 (4,700); NMR ($CF_3CO_2H$) 3·55 3H s (NMe); 3·8 5H complex (aliphatic protons); 4·05 6H s (2×OMe); 6·9 1H m (olefinic); 7·35 1H s ($C_5-H$); 7·75 1H s ($C_8-H$). (Found: C, 62·3; H, 5·1; N, 4·1. $C_{18}H_{17}NO_6$ requires: C, 62·9; H, 5·0; N, 4·1%.)

(b) p-*Benzoquinone.* (i) A soln of **16a** (0·5 g) in AcOH (20 ml) containing *p*-benzoquinone (0·5 g) was heated under reflux for 6 hr. The product **5c** crystallised on cooling (0·5 g; 72%) m.p. 280°, $\nu_{max}$ cm$^{-1}$ 1660, 1650, 1610, *m/e* (% base peak) 319 (100); 302 (5); 301 (32); 295 (5); 291 (22); 290 (41); 248 (8); 247 (19). (Found: C, 71·9; H, 4·1; N, 4·5. $C_{19}H_{13}NO_4$ requires: C, 71·5; H, 4·07; N, 4·4%.)

(ii) In a similar way **15b** gave the adduct **5d** in 67% yield, m.p. > 320° from AcOH, $\nu_{max}$ cm$^{-1}$ 1670, 1642, $\lambda_{max}$ nm ($\epsilon_{max}$) 202 (21,400); 254 (13,400); NMR ($CF_3CO_2H$) 3·75 3H s (NMe); 4·15 6H d (2×OMe); 7·30 2H s ($C_2-H+C_3-H$); 7·90 1H s ($C_{10}-H$); 8·15 1H s ($C_7-H$); 8·30 1H d ($J=8·0$ Hz) ($C_{11}-H$); 8·75 1H d ($J=8·0$ Hz) ($C_{12}-H$). (Found: C, 68·6; H, 4·5; N, 3·9. $C_{20}H_{15}NO_5$ requires: C, 68·8; H, 4·3; N, 4·0%.)

(c) *Propiolic acid.* A soln of **15a** (0·5 g) and propiolic acid (1·0 g) in xylene (40 ml) and AcOH (5 ml) was heated under reflux for 16 hr. The soln was concentrated and the pale yellow product **6b** (0·29 g) m.p. 177–180° was collected, $\nu_{max}$ cm$^{-1}$ 3280, 1690, 1650, 1610, *m/e* (% base peak) 286 (16); 285 (100); 284 (12); 268 (8); 266 (4); 255 (34); 254 (12); 238 (20); 237 (88); 212 (6); 211 (26); 210 (10); 209 (18); 168 (12); 140 (8); 139 (22) metastables 228·3 (285→255); 174·5 (255→211); 220·2 (255→237); 184·2 (237→209). (Found: C, 67·1; H, 5·4; N, 5·0. $C_{16}H_{15}NO_4$ (285) requires: C, 67·4; H, 5·26; N, 4·9%.)

4-(7-*Methoxyisoquinolyl*)*acetic acid* (**16a**). The acetal **7a** (5·0 g) in 6N HCl (100 ml) was left overnight at room temp. After warming on steam bath for 15 min glyoxylic acid (2·2 g) in 2N HCl (10 ml) was added. After 1 hr on the water bath the mixture was left overnight at room temp. The soln was concentrated under reduced pressure when the required **16a** was obtained as yellow crystals (3·7 g; 65%). m.p. 209–211°, $\nu_{max}$ cm$^{-1}$ 3360, 1746, 1632. (Found: C, 56·3; H, 5·1; N, 5·0; Cl, 13·1. $C_{12}H_{12}NO_3$.HCl requires: C, 56·8; H, 4·73; N, 5·5; Cl, 14.0%.)

Ethyl ester methiodide **19a** m.p. 117–119° from acetone (Found: C, 46·5; H, 5·1; N, 3·5; I, 33·2. $C_{15}H_{18}NO_3I$ requires: C, 46·55; H, 4·7; N, 3·6; I, 32·8%).

*Ethyl-4-(6,7-dimethoxyisoquinolyl)acetate hydrochloride.* A soln of 4-(6,7-dimethoxyisoquinolyl) acetic acid[3] hydrochloride (2·0 g) in abs EtOH (35 ml), saturated with HCl gas, was heated under reflux for 6 hr, then allowed to cool overnight. The white solid was collected and recrystallised from EtOH—HCl m.p. 193–194°, *m/e* (% base peak): 276 (10); 275 (64); 203 (16); 202 (100); 159 (3); 158 (7); 157 (6), metastables at 148·4 (276→202). (Found: C, 58·0; H, 5·7; N, 4·5; Cl, 11·7. $C_{15}H_{18}NO_4Cl$ requires: C, 57·8; H, 5·78; N, 4·5; Cl, 11·4%). Methiodide **19b** m.p. 169–171° from acetone. (Found: C, 46·5; H, 5·1; N, 3·5. $C_{16}H_{20}NO_4I$ requires: C, 46·1; H, 4·8; N, 3·4%.)

*β-4-(6,7-Dimethoxyisoquinolyl) ethanol* (**17b**). LAH (1·5 g) was added to a soln of the above ester (2·5 g) in THF (150 ml). The mixture was stirred at room temp for 4 hr then treated with 10% sodium potassium tartrate soln. After decanting, the organic layer was dried and evaporated to leave **17b** (1·6 g; 76%) as a white solid, $\nu_{max}$ cm$^{-1}$ 3280, 1630, 1600, 1580; NMR ($CDCl_3$) 3·15 2H t ($-CH_2-CH_2$); 3·95 6H s (2×OMe); 4·3 1H s (OH, removed by $D_2O$); 4·0 2H m ($-CH_2-CH_2$); 7·05 1H s ($C_3-H$); 7·18 1H s ($C_8-H$); 8·08 1H s ($C_3-H$); 8·63 1H s ($C_1-H$); *m/e* (% base peak) 234 (9); 233 (100); 203 (17); 202 (50), metastable 175·0 (233→202). (Found: C, 66·8; H, 6·0; N, 6·0. $C_{13}H_{15}NO_3$ requires: C, 67·0; H, 6·44; N, 6·0%.)

*Simultaneous enol acetylation and diene additions of 2-methyl-4-acetylisocarbostyril*

(a) *With maleic anhydride.* A soln of **21c** (1·0 g), maleic anhydride (0.7 g) and *p*-toluenesulphonic acid (25 mg) in isopropenyl acetate (50 ml) was heated under reflux for 24 hr and then cooled. The precipitated adduct **22** (1·2 g) was collected and crystallised from a large volume of acetonitrile, m.p. 291–293°, $\nu_{max}$ cm$^{-1}$ 1840, 1760, 1750, 1640 , *m/e* 342, 299, 271, 225 and 201. (Found: C, 63·3; H, 4·7; N, 4·1. $C_{16}H_{15}NO_6$ requires: C, 63·3; H, 4·4; N, 4·1%).

(b) *With* p-*benzoquinone.* A soln of **21c** (1·0 g), *p*-benzoquinone (1·0 g) and *p*-toluenesulphonic acid (25 mg) in isopropenyl acetate (50 ml) was heated under reflux for 48 hr. Work up as above gave the adduct **24** (1·1 g) m.p. 203–205°, $\nu_{max}$ cm$^{-1}$ 1750, 1670, 1640, *m/e* 351 ($M^+$); 243 ($M^+-p$-benzoquinone); 309 ($M^+-C_2H_2O$); 293 ($M^+-CH_3CO_2H$); 201. (Found: C, 67·9; H, 5·0; N, 3·9. $C_{20}H_{17}NO_5$ requires: C, 68·4; H, 4·9; N, 4·0%).

*The dihydro adduct* (**25**). Zn dust (1·0 g) was added in small portions to a refluxing soln of the above adduct (500 mg) in AcOH (25 ml). After 1 hr at reflux, the mixture was filtered, and the filtrate poured into water. Solid $NaHCO_3$ was added until efferescence ceased, and the product was extracted into $CHCl_3$. After the usual work up the solid was recrystallised from EtOH to give the dihydro adduct **25** m.p. 210–212°, $\nu_{max}$ cm$^{-1}$ 1750, 1710, 1640, *m/e* 353 ($M^+$); 311 ($M^+$−keten); 295 ($M^+$−acetic acid). (Found: C, 67·7; H, 5·4; N, 3·9. $C_{20}H_{19}NO_5$ requires: C, 68·0; H, 5·4; N, 4·0%.)

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## REFERENCES

[1]S. F. Dyke, M. Sainsbury, D. W. Brown and R. D. J. Clipperton, *Tetrahedron* **26**, 5969 (1970)
[2]E. Schlittler and J. Mueller, *Helv. Chim. Acta* **31**, 914 (1948)
[3]S. F. Dyke, M. Sainsbury and B. J. Moon, *Tetrahedron* **24**, 1467 (1968); *J. Chem. Soc.* (C), 1797 (1970)
[4]C. M. Cimarusti and J. Wolinsky, *J. Am. Chem. Soc.* **90**,

113 (1968); R. B. Login and J. Wolinsky, *J. Org. Chem.* **35**, 1986 (1970)
[5]D. E. Horning, G. Lacasse and J. M. Muchouski, *Canad. J. Chem.* **49**, 2785 (1971)
[6]R. Mercher and L. Wolff, *Liebigs Ann.* **399**, 278 (1913)
[7]M. Sainsbury, D. W. Brown, S. F. Dyke and G. Hardy, *Tetrahedron* **25**, 1881 (1969)
[8]J. M. Bobbitt, *Advances in Heterocyclic Chemistry* (Edited by A. R. Katritsky and A. J. Boulton) Vol. 15, Academic Press, New York, (1973)