Tetrahedron Vol. 35, pp. 1861–1867

0040-4020/79/0801-1861/$02.00/0

1,2-DIHYDROISOQUINOLINES—XXI[1]
VINYLOGOUS MEERWEIN SALTS

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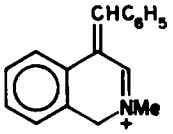
(*Received in the UK 20 October 1978*)

Abstract—Treatment of 4-acyl-1,2-dihydroisoquinolines with the Meerwein reagent (triethyloxonium tetrafluoroborate) produces vinylogues of the ethoxyimminium cations in high yield. With a view to developing syntheses of 3-substituted isoquinoline derivatives, some reactions of these salts with nucleophilic reagents have been examined.

The usual isoquinoline ring syntheses[2] are satisfactory for derivatives with electron-donating groups at positions C_5–C_8, and for 1- and 4-substituted compounds. Isoquinolines substituted at C_3 may still be very difficult to prepare, especially when 7,8-dioxygenation is required as well.[3] Although in principle 1,2-dihydroisoquinolines should be susceptible to nucleophilic attack at C_3[4], in practice the only successful examples have been intramolecular in nature.[4,5] However, the 4-benzylidene-1,4-dihydroisoquinoline **1** has been converted into **2** with methyl magnesium iodide,[6] and the compound **4** resulted when **3** was treated with KCN,[7] but yields in both cases were very poor.



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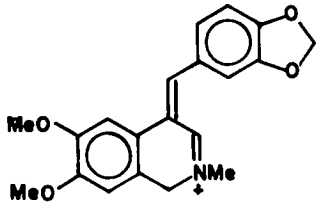

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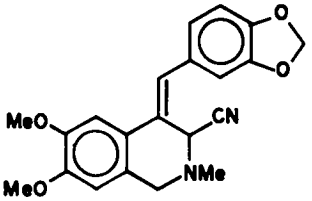

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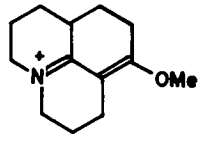
Since imminium salts are readily prepared[8,9] from amides by the action of triethyloxonium tetrafluoroborate, and since these salts are susceptible to attack by nucleophiles at the electron-deficient carbon atom, it occurred to us that a vinylogous Meerwein salt may be a useful intermediate in the isoquinoline series. Such compounds would be expected to be attacked by nucleophiles either at C_3 or at C_9 (see structure **8** for numbering system). Vinylogous Meerwein salts have not been widely studied, although in one relevant example,[10] the salt **5** was converted into **6** with the isobutyl grignard reagent.



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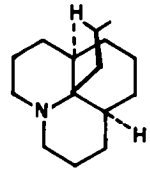

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2-Methyl-4-formyl-1,2-dihydroisoquinoline **7a** is readily available[11] and we have now found that this can be converted into the salt **8b** by treatment with the Meerwein reagent in CH_2Cl_2 solution. Crystallisation of **8b** from methanol gave **8a** in pure form. The stereochemistry shown was assigned upon the basis of proton NMR chemical shift data on a series of compounds, and this is discussed later. However, the low field multiplet at 8.5 is assigned to C_5–H which is deshielded by the $\Delta^{4,9}$ double bond. In the mass spectrum, loss of 15 units gave the ion "a" (Scheme 1), the further fragmentations of which are identical to those observed with **7a**. Further support for structure **8a** was provided by the fact that hydrolysis with hot, dilute hydrochloric acid gave the vinylogous amide **7a** in almost quantitative yield.

When **8a** was reacted with phenyl magnesium bromide in ether at room temperature, followed by heating, a base was isolated in 82% yield, and characterised as the methiodide. The UV spectrum of the base (λ_{max} 270 nm) indicated much less conjugation than exhibited by **8a** itself (λ_{max} 284 and 345 nm). In the IR spectrum a band at 1650 cm^{-1} suggested the presence of an exocyclic methylene group, whereas the proton NMR spectrum exhibited signals attributed to a tertiary *N*-Me group (2.2δ, singlet), a methoxyl group (3.45δ, singlet) and a one-proton multiplet at 8.3δ due to C_5–H; *eight* other aromatic protons were indicated by a multiplet in the range 6.8–7.9δ. Structure **9a** for this base is compatible with these data, and it was further supported by the mass spectral fragmentation pattern summarised in Scheme 2. It has not proved possible to assign stereochemistry about the double bond in any of the derivatives **9a–9c**. In the proton NMR of the methiodide the *N*-methyl groups resonate as singlets at 3.1 and 3.27δ, due to the differential shielding provided by the C_3-phenyl group.

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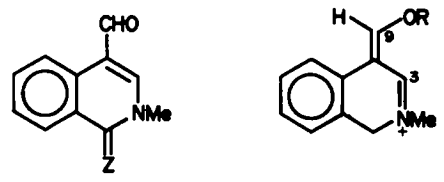
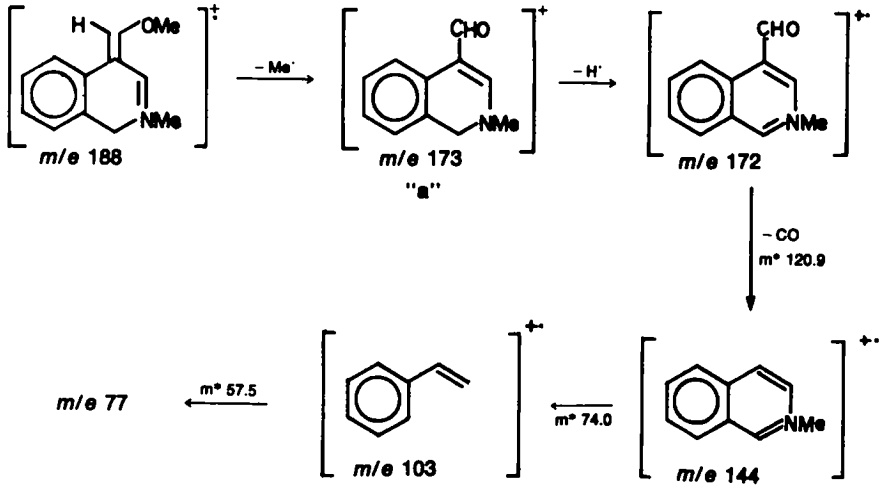
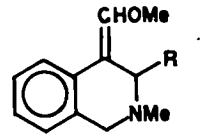


7a: Z = 2H
7b: Z = O

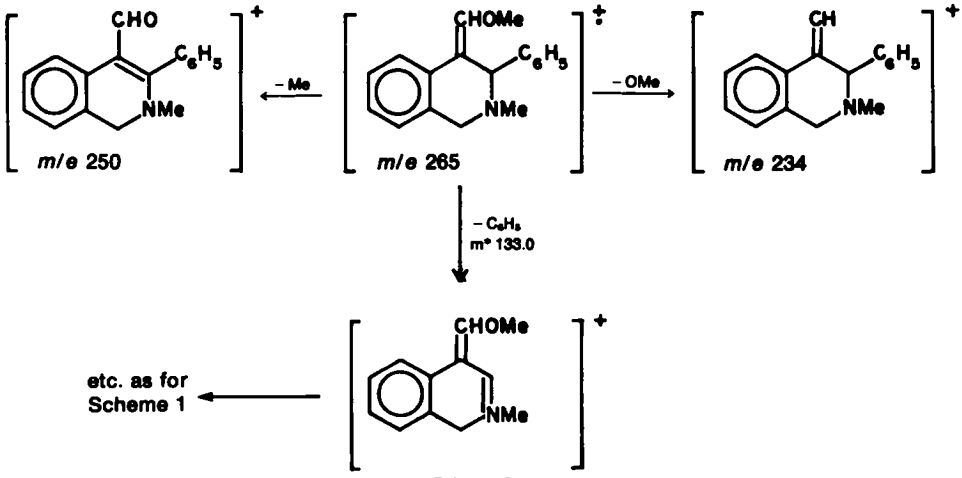
8a: R = Me
8b: R = Et



Scheme 1.

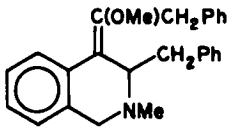


9a: R = C_6H_5
9b: R = $CH_2C_6H_5$
9c: R = Et



Scheme 2.

When benzyl magnesium bromide was reacted, at room temperature, with **8a** a basic yellow oil was produced in 40% yield and the compound was characterised as the methiodide of **10**. The UV spectrum is similar to that of **9a**, but the mass spectrum indicated the presence of two benzyl groups. In the proton NMR spectrum the C_5–H resonates at a lower field than the other protons on the ring, so an exocyclic double bond is indicated. Repetition of the reaction with restricted amounts of grignard reagent gave a light brown oil from which **10** was isolated upon trituration with ether. The residual oil, characterised as the methiodide, was the



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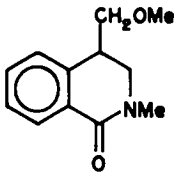

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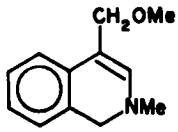
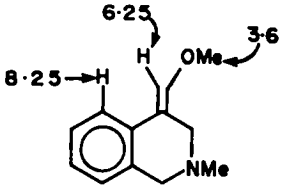


13

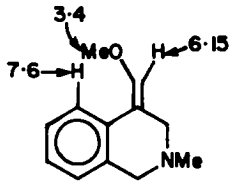
expected product **9b**. The NMR spectral data are compatible with this, and the mass spectral fragmentations are closely similar to those for **9a** (Scheme 2).

With ethyl magnesium bromide, **8a** reacted to give the expected **9c**, characterised as the methiodide. The mass spectrum closely parallels the spectra of **9a** and **9b**.

When the vinylogous Meerwein salt **8a** was reacted with LAH in THF under reflux, five compounds were isolated by chromatography over neutral alumina and were identified as **7a**, **7b**, **11**, and **12** as an inseparable mixture of geometrical isomers **12a** and **12b**. The figures refer to the proton chemical shifts and the ratio of **12a**: **12b** was found to be 4:1 as deduced from integral

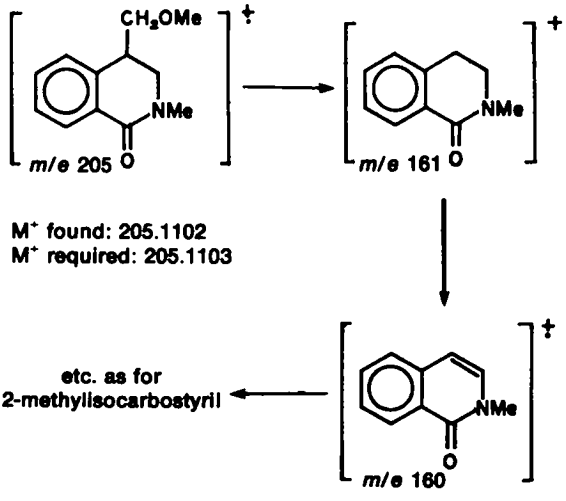


12a



12b

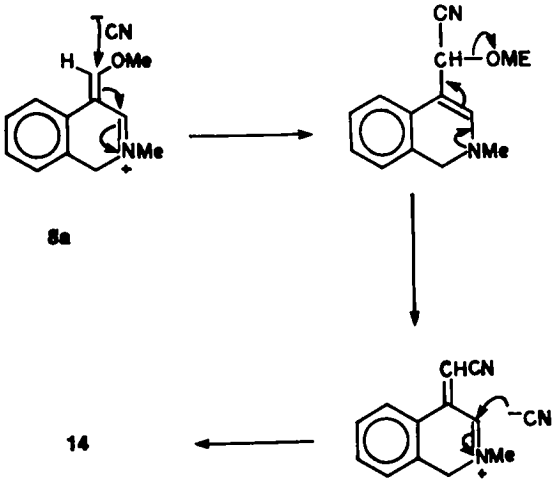
measurements on the spectrum. A high resolution mass measurement on the $(M-1)^+$ ion **8a** from **12** gave 188.1706 (calculated: 188.1075). The remaining fragmentations were found to be identical to those of **8a** itself. The structure of **11** was deduced from mass spectral data, summarised in Scheme 3. Presumably oxidation of the C_1-methylene group occurs during column chromatography. When a methanolic solution of **8a** was heated under reflux with $NaBH_4$, a mixture of **7a**, **7b** and **12** was again produced. Thus, it is apparent that H^- ion can attack **8a** at C_9 to yield the 1,2-dihydroisoquinoline **13** followed by further reduction.



Scheme 3.

One further nucleophilic reagent, KCN, was reacted with **8a**. Chromatography of the resultant yellow gum over neutral alumina gave **7a** and **7b** as pure components, together with a binary mixture, shown by NMR and mass spectral studies to be **14** and **15**. This result is most easily explained by initial attack of CN^- at C_9 (Scheme 4).

Hence it seems that nucleophiles can attack **8a** either at C_3 or at C_9, followed by further, complex, reaction pathways. The rates of these two processes are comparable for **8a**. Attention was then turned to a C_3-substituted vinylogous Meerwein salt in the hope of achieving more clear-cut reactions.

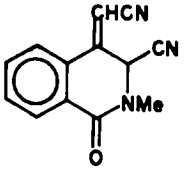


8a

Scheme 4.

14

(M-1)+ Found: 208.0874
Required: 208.0875



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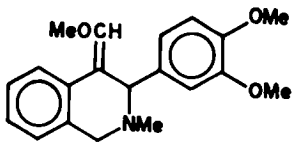
M+ Found: 223.0743
Required: 223.0746

As part of a programme in the benzo[c]phenanthridine alkaloids[12] the 3-arylisocarbostyril **16a** was prepared as a model compound by the method outlined in Scheme 5. The method described by Dorofeenko *et al.*[13] to prepare the isocoumarin (**16a** with NMe replaced by oxygen) failed in our hands. Horning *et al.*[14] have found that 2-methylisocarbostyril undergoes electrophilic substitution at C_4 and they prepared the 4-acetyl derivative under Friedel–Craft conditions. However, our attempts to acylate **16a** under these conditions failed. Reduction of **16a** with LAH gave the 1,2-dihydroisoquinoline **16b** as a stable solid, but attempts to acylate it at C_4 also failed. However, the Vilsmeier reaction was successful, and **16c** was isolated in 83% yield. To close ring C of a

benzo[c]phenanthridine required an additional carbon atom in the C_4-side chain of **16c** but none of the more usual methods was successful. However, **16c** was easily converted into the vinylogous Meerwein salt **17b** under the conditions used to prepare **8b**, and, when crystallised from methanol the product was **17a**. In the proton NMR spectrum of **17a** the C_9-OMe group resonates at the relatively high field of 3.2δ. This is attributed to the shielding effect of the C_3-aryl substituent (see **18**). The C_9-H resonance, at 7.1δ, is accounted for by the deshielding effect of the aromatic ring A. Since the C_9-H of **8a** also resonates at 7.1δ and the C_9-OMe absorbs at 3.35δ, the geometry about the $\Delta^{4,9}$ double bond is assigned as shown in **8a**. In **8b** the C_9-H resonance appears at 7.2δ, whereas the *O*-ethyl group resonates at 1.15δ (CH_3–CH_2) and 3.5δ (CH_3–CH_2–).

Reduction of **17a** with LAH gave the expected base **19**



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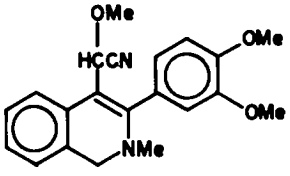

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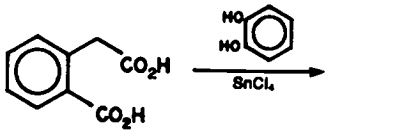
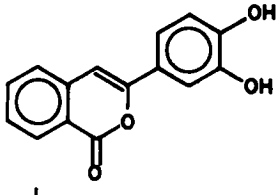
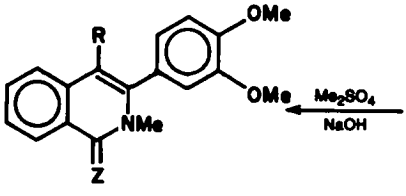
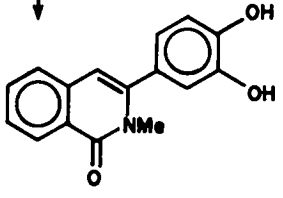
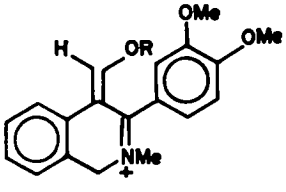




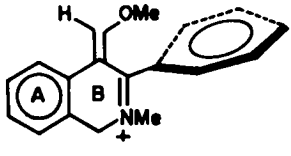




16a: Z = O; R = H
16b: Z = 2H; R = H
16c: Z = 2H; R = CHO
16d: Z = O; R = CHO



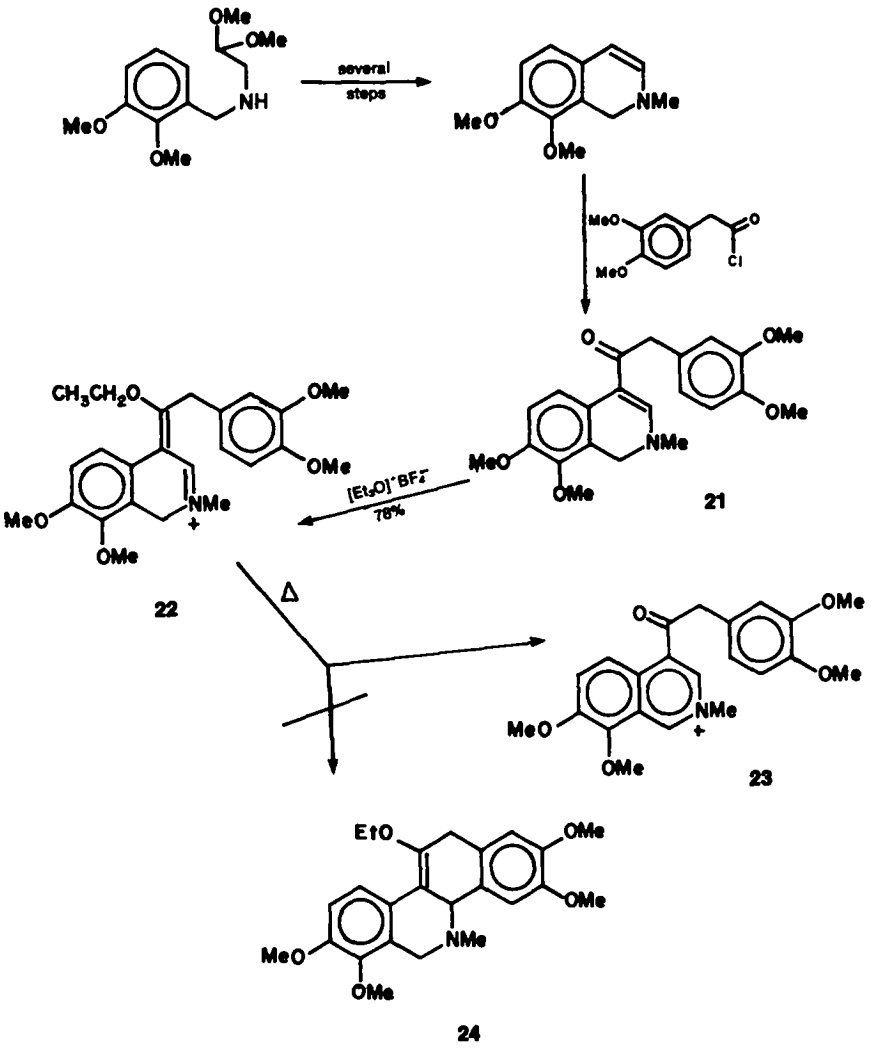
17a: R = Me
17b: R = Et



18

in very poor yield. It was hoped to hydrolyse **19** to the 1,2,3,4-tetrahydroisoquinoline-4-aldehyde, but the yield of **19** was so low that this route was abandoned. The vinylogous Meerwein salt **17a** was reacted with KCN and the required product **20** was obtained in 86% yield. The proton NMR spectrum contained a 7-hydrogens multiplet at 6.7–7.6δ attributed to all the aromatic protons, together with signals due to C_9-H (4.6δ), C_9-OMe, 2 × ArOMe and NMe groups. Various attempts were made to convert **20** into a benzo[c]phenanthridine derivative, but without success.

One final attempt was made to utilise the properties of vinylogous Meerwein salts of the isoquinoline series in the synthesis of benzo[c]phenanthridine. The Meerwein salt **22** was synthesised[15] via **21** as shown in Scheme 6. The geometry about the exocyclic double bond is allocated as shown because the *O*-ethyl group signals in the proton NMR (CH_3 centred at 1.5δ and CH_2 at 4.4δ) are deshielded in comparison to the corresponding resonances in **8b**. All attempts to achieve the thermal ring closure of **22** to **24** failed; the major product was the 4-acylisoquinolinium salt **23**.



Scheme 6.

EXPERIMENTAL

UV spectra refer to EtOH solutions unless otherwise stated, IR spectra were measured on Nujol mulls. Proton NMR spectra were recorded at 60 or 100 MHz and chemical shifts are measured in ppm downfield from internal TMS. M.ps are uncorrected. Mass spectra were recorded at low resolution on AEI MS 12 and the high resolution mass measurements were carried out on AEI MS 902 instrument.

4-Formyl-2-methyl-1,2-dihydroisoquinoline **7a**. (a) LAH (1.0 g) was added, portionwise, to a stirred slurry of isoquinoline methiodide (10.0 g) in dry ether (100 ml) under a nitrogen atmosphere. After 90 min the excess LAH was decomposed with ethyl acetate (2.3 g) and then sodium potassium tartrate solution. The 1,2-dihydro compound was separated twice into ether and the combined extracts dried over anhydrous $MgSO_4$ (under nitrogen). The dihydroisoquinoline in ether was added slowly to a solution of $POCl_3$ (6.0 g) and DMF (5.0 g) which had been stirred at 0° for 30 min, then cooled in an ice/salt bath; the temperature was kept below 5° during the addition. The ice bath was replaced by a water bath at 50° until all the ether had distilled (1–1.5 h). Crushed ice (150 g) was added to the red viscous residue, then the mixture was basified with NaOH (40 g in 80 ml H_2O) with cooling. Water (100 ml) was added to the yellow solution when a solid crystallised. Recrystallisation from ethanol/water gave **7a** as light yellow plates (3.9 g; 31%) m.p. 129–130° (lit.[11] m.p. 130°).

4-Ethoxymethylene-2-methyl-1,4-dihydroisoquinoline tetrafluoroborate **8b**. The compound **7a** (2.0 g) was dissolved in dry dichloromethane (75 ml) and triethyloxonium tetrafluoroborate (2.5 g) added to the stirred solution. After 40 min, the solvent was evaporated under reduced pressure and the white solid product was recrystallised from ethanol to give **8b** as pale lemon needles (0.98 g; 30%) m.p. 200–201°. ^{1}H NMR (d_6-DMSO), 8.55 (1H, s, C_5–H), 8.35 (1H, m, C_3–H), 7.9 (1H, s, ), 7.35–7.1 (3H, m, C_6–H + C_7–H + C_8–H), 5.1 (2H, s, 2 × C_1–H), 4.35 (2H, q, J = 6Hz, O–CH_2–CH_3), 3.6 (3H, s, N–CH_3), 1.3 (3H, t, J = 6Hz, O–CH_2–CH_3). (Found: C, 62.8; H, 5.6; N, 4.6. $C_{13}H_{16}NOBF_4$ requires: C, 63.0; H, 5.5; N, 4.8%).

4-Methoxymethylene-2-methyl-1,4-dihydroisoquinolinium tetrafluoroborate **8a**. Recrystallisation of **8b** from methanol gave **8a** as pale lemon needles, m.p. 220–222° (81% from **7a**). ν_{max} 1675; 1625, 1220 cm^{-1}. λ_{max} nm (ϵ_{max}) 235 (6100), 284 (8700) and 345 (6600). ^{1}H NMR (d_6-DMSO) 8.5 (m, 1H, C_5–H); 8.0 (m, 1H, C_3–H); 7.75 (s, 1H, C_9–H); 7.5–7.1 (m, 3H, C_6–H + C_7–H + C_8–H); 5.05 (s, 2H, 2 × C_1–H); 4.3 (s, 3H, OMe); 3.6 (s, 3H, NMe). MS (% base peak) *m/e* 188 (11) (M^+), 173 (55), 172, 144, 103, 77 m* 120.9, 74.0, 57.5. [Found: C, 52.2; H, 5.3; N, 5.1. $C_{12}H_{14}NOBF_4$ requires: C, 52.5; H, 5.1; N, 5.1%].

Hydrolysis of **8a** to **7a**. The vinylogous Meerwein salt **8a** (400 mg) was dissolved in dilute hydrochloric acid and heated on a steam bath for 30 min. The neutralised solution was extracted into ether, dried over anhydrous $MgSO_4$ and the solvent removed under reduced pressure, to afford **7a** (195 mg; 78%), m.p. 130°, mixed m.p. 129–131°.

4-Methoxymethylene-2-methyl-3-phenyl-1,2,3,4-tetrahydroisoquinoline **9a**. Phenyl magnesium bromide (prepared from bromobenzene (3.10 ml), magnesium (2.0 g) in ether (100 ml) was added dropwise to the imminium tetrafluoroborate **8a** (1.0 g) suspended in ether (50 ml) under N_2. After 12 h at r.t., the mixture was heated under reflux for 6 h, then cooled and poured onto ice cold NH_4Cl (10.0 g) in water (100 ml). After making alkaline with NH_3, the mixture was extracted into ether and normal work up gave a brown oil (790 mg; 82%). ^1H NMR ($CDCl_3$), 8.15 (s, 1H, C_5–H); 7.5–6.5 (m, 9H, aromatic protons + C_9–H); 5.90 (s, 1H, C_3–H); 4.0 (s, 2H, $2\times C_1$–H); 3.45 (s, 3H, OMe); 2.20 (s, 3H, NMe). The methiodide crystallised from acetone as off-white needles, m.p. 161–162°. ^1H NMR (d_6-DMSO): 8.3 (s, 1H, C_5–H); 7.6–7.3 (m, 8H, aromatic H's); 6.85 (s, 1H, C_9–H); 5.7 (s, 1H, C_3–H); 4.55 (q, 2H, $2\times C_1$–H); 3.90 (s, 3H, OMe); 3.28 (s, 3H) and 3.1 (s, 3H) ($2\times$ NMe). MS 265 (M^+); 250, 234, 188 m* 133. (Found: C, 55.7; H, 5.5; N, 3.3. $C_{19}N_{22}NOI$ requires: C, 56.0; H, 5.4; N, 3.4%).

4 - (9 - Methoxy - 9 - benzyl)methylene - 3 - benzyl - 2 - methyl - 1,2,3,4-tetrahydroisoquinoline **10**. The Meerwein salt **8a** (1.0 g) was added portionwise to benzyl magnesium bromide (from 2.27 g benzyl bromide) in ether (50 ml). After 12 hr at r.t. the mixture was heated under reflux for 6 hr, then cooled and the product worked up for basic material to give a pale brown oil (530 mg; 40%). Methiodide m.p. 189–190° from acetone. ^1H NMR (d_6-DMSO) contained 3.6 (s, 3H, OMe); 3.15 (3H) and 3.45 (3H) ($2\times \overset{+}{N}$Me). (Found: C, 88.0; H, 7.1; N, 4.1. $C_{26}H_{27}NO$ requires: C, 88.3; H, 7.7; N, 4.0%).

2 - Methyl - 3 - benzyl - 4 - methoxymethylene - 1,2,3,4 - tetrahydroisoquinoline **9b**. A solution of benzyl magnesium bromide (from 2.27 g benzyl bromide) in ether (50 ml) was added dropwise to a suspension of **8a** (1.0 g) in ether (30 ml) under N_2. After 12 hr at r.t. standard work-up gave an oil (1.27 g; 98%), methiodide m.p. 181–182° from acetone. ν_{max} cm^{-1} 1640 (>C=C<), 1250 (C=C–O–C–), 1070 (–C–O–C–). ^1H NMR (d_6 DMSO): 8.15 (s, 1H, C_5–H); 7.5–7.1 (m, 8H, aromatic H's); 5.9 (s, 1H, C_9–H); 4.9 (m, 1H, C_3–H); 4.35 (m, 2H, $C_6H_5CH_2$–); 3.40 (s, 3H, OMe); 3.1 (s, 3H, NMe). MS *m/e* 294 (M^+), 293, 248, 247, 246 (base peak), 217, 188, 158, 142, 127. (Found: C, 55.9; H, 5.3; N, 3.4. $C_{19}H_{21}NOI$ requires: C, 56.1; H, 5.2; N, 3.1%).

2 - Methyl - 3 - ethyl - 4 - methoxymethylene - 1,2,3,4 - tetrahydroisoquinoline **9c**. Ethyl magnesium bromide (4.0 g) in ether (50 ml) was added dropwise to **8a** (1.0 g) in ether (30 ml) under N_2. The remainder of the procedure was exactly similar to **9b** above, to give a brown oil (0.88 g; 99%). Methiodide m.p. 141–143° from acetone (Found: C, 48.4; H, 5.2; N, 3.9. $C_{14}H_{19}NOI$ requires: C, 48.9; H, 5.5; N, 4.1%). Chromatography of the base over neutral alumina gave **9c** as a pale oil, one spot on tlc. ^1H NMR (d_6 DMSO): 8.1 (s, 1H, C_5–H); 7.3–7.0 (m, 3H, aromatic H's); 6.10 (s, 1H, C_9–H); 4.4–4.0 (q, J = 7.0 Hz, 2H, $-\underline{CH_2}CH_3$); 3.4 (s, 1H, C_3–H); 3.7 (s, 3H, OMe); 2.4 (s, 3H, NMe); 0.85 (t, J = 7.0 Hz, 3H, $\underline{CH_3}CH_2$).

Reduction of **8a** *with lithium aluminium hydride.* LAH (0.2 g) was added portionwise to a stirred suspension of **8a** (0.8 g) in THF (50 ml) under nitrogen. After heating the mixture under reflux for 3 hr excess LAH was decomposed with NaK tartrate solution and the THF layer was dried and evaporated to leave a brown oil. Chromatography over neutral alumina and elution with 20% $CHCl_3$/pet.ether (60–80) gave four fractions. Two of these were identified (superimposable IR spectra) as **7a** and **7b** whilst the third gave a *compound* as a pale oil which was identified as 2-methyl-4-methoxymethyldihydroisocarbostyril **11** (M^+ found: 205.1102; $C_{12}H_{15}NO_2$ requires: 205.1103). The fourth fraction proved to be an inseparable mixture of the geometrical isomers of 2-methyl-4-methoxymethylene-1,2,3,4-tetrahydroisoquinoline **12a + 12b**. ν_{max} 1660 cm^{-1} (>C=C<). ^1H NMR ($CDCl_3$) (i) for **12a**: 8.25 (m, C_5–H); 6.25 (s, C_9–H); 3.6–3.9 (m, OMe + $2\times C_1$–H + $2\times C_3$–H); 2.45 (s, NMe) and (ii) for **12b** 7.6 (m, C_5–H); 6.15 (s, C_9–H); 3.6–3.9 (m, OMe + $2\times C_1$–H + $2\times C_3$–H); 2.4 (s, NMe). (Found: C, 83.0; H, 8.4; N, 7.9. $C_{12}H_{15}NO$ requires: C, 83.2; H, 8.7; N, 8.1%). $((M-1)^+$ found: 188.1076 $C_{12}H_{14}NO$ requires: 188.1075).

Reaction of **8a** *with KCN.* KCN (0.25 g) was added to a stirred solution of **8a** (0.8 g) in 95% EtOH (60 ml) under N_2. After stirring at r.t. 16 hrs, the mixture was heated under reflux 1 hr, then solution evap. to dryness under reduced pressure to yield a gum which was chromatographed over neutral alumina and eluted with 60% $CHCl_3$/pet.ether (60–80°). Four components were isolated, the first two were identical (superimposable IR spectra) with authentic samples of **7a** and **7b**. The third fraction gave the compound **14** as a pale oil ($(M-1)^+$ found: 208.0874; $C_{13}H_{10}N_3$ required 208.0874) ^1H NMR ($CDCl_3$): 7.8 (m, 1H, C_5–H); 7.1 (m, 4H, aromatic H's); 3.8 (s, 1H, C_3–H); 3.0 (s, 3H, NMe). (Found: C, 74.8; H, 5.1; N, 20.1. $C_{13}H_{11}N_3$ requires: C, 74.6; H, 5.3; N, 20.1%).

The fourth fraction from the column gave **15** as a pale yellow oil [(M^+) found: 223.0743; $C_{13}H_9N_3O$ requires: 223.0746]. ^1H NMR ($CDCl_3$) 8.8 (m, 1H, C_6–H); 7.8 (m, 1H, C_5–H); 7.2 (m, 3H, aromatic H's); 3.8 (s, 4H, C_3–H + NMe).

3-(3,4-Dimethoxyphenyl-2-methylisocarbostyril **16a**. Homophthalic acid (40.0 g) and catechol (26.4 g) were added with stirring to stannic chloride (100 ml) and the mixture was slowly raised to reflux temp., and maintained there for 90 min. The complex was decomposed with 2N HCl and the mixture was steam distilled to remove the excess catechol. This left 3-(3,4-dihydroxyphenyl)-isocoumarin as a purple solid, which was collected (ν_{max} cm^{-1}, 3300, 1690, 1635). The isocoumarin, without further purification, was heated under reflux in ethanol (500 ml) with an ethanolic solution (35%) of methylamine (150 ml) for 8 hr, additional methylamine (10 ml) being added each hour. Evaporation of the solvent under reduced pressure yielded (3-(3,4-dihydroxyphenyl)-2-methylisocarbostyril as a grey solid. (ν_{max} cm^{-1}, 3250, 1640). The isocarbostyril, without purification, was dissolved in 10% aqueous sodium hydroxide solution (150 ml) and heated on a steam bath. Dimethyl sulphate (20 ml) was added dropwise over 1 hr and the solution was heated for a further 2 hr, additional dimethyl sulphate (3 ml) being added every 30 min. During this reaction the solution was kept basic by adding 10% aqueous sodium hydroxide. On cooling the solid product was collected and recrystallised from ethanol (charcoal) as colourless cubes m.p. 173–174° (21.0 g, 32%). ν_{max} cm^{-1}, 1650, 1624. λ_{max} nm (ϵ), 207 (51,800), 295 (16,700). ^1H NMR ($CDCl_3$): 3.5 (s, 3H, N–CH_3), 3.95 (s, 6H, $2\times$–OCH_3), 6.5 (s, 1H, C_6–H), 8.5 (m, 1H, C_8–H), 6.9–7.7 (complex, 6H, remaining aromatic protons). (Found: C, 73.2; H, 5.8; N, 4.7. $C_{18}H_{17}NO_3$ requires: C, 73.3; H, 6.0; N, 4.8%).

3-(3,4-Dimethoxyphenyl)-2-methyl-1,2-dihydroisoquinoline **16b**. LAH (2.0 g) was added portionwise to a stirred solution of 3-(3,4-dimethoxyphenyl)-2-methylisocarbostyril (5.0 g) in THF (125 ml), and the resulting suspension was stirred for 3 hr, after which the excess LAH was decomposed with sodium potassium tartrate solution. The mixture was filtered, and the filtrate was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The solid product was recrystallised from ethanol as colourless plates m.p. 86–88° (4.4 g, 92%). ν_{max} cm^{-1}, 1595. λ_{max} nm (ϵ), 205 (31,200), 280 (9,600), 349 (15,200). ^1H NMR ($CDCl_3$) 2.6 (s, 3H, N-CH_3), 3.9 (s, 6H, $2\times OCH_3$), 4.3 (s, 2H, N–CH_2–), 5.85 (s, 1H, C_6–H), 6.8–7.3 (complex, 6H, aromatic protons). (Found: C, 76.6; H, 6.7; N, 5.0. $C_{18}H_{19}NO_2$ requires: C, 76.8; H, 6.8; N, 5.0%).

4 - Formyl - 3 - (3,4 - dimethoxyphenyl) - 2 - methyl - 1,2 - dihydroisoquinoline **16c**. Phosphorus oxychloride (1.44 g) was added dropwise with stirring to DMF (2.74 g) cooled in an ice-salt bath and the resulting mixture was stirred at 0° for 30 min. 3-(3,4-Dimethoxyphenyl)-2-methyl-1,2-dihydroisoquinoline(2.4 g) in chloroform (10 ml) was added dropwise to the stirred solution at 0°, and after addition was complete the temperature of the resulting mixture was slowly raised to 65° and maintained there for 16 hr. The solvent was then removed under reduced pressure and the gum was cautiously quenched with water (100 ml), basified with 30% aqueous NaOH solution and extracted with chloroform (3×50 ml). The combined chloroform extracts were washed with water (40 ml), dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The solid product was recrystallised from ethanol as white needles, m.p. 174–176° (2.2 g, 83%). ν_{max} cm^{-1}, 1625. λ_{max} nm (ϵ), 228 (17,500), 290 (13,900), 354 (10,600). ^1H NMR ($CDCl_3$): 2.9 (s, 3H, N–CH_3), 3.9 (s, 3H,

-OCH_3), 3.95 (s, 3H, -OCH_3), 4.6 (s, 2H, N-CH_2-), 8.7 (m, 1H, C_5-H), 5.75–6.35 (complex, 6H, remaining aromatic protons), 9.0 (s, 1H, -CHO). (Found: C, 73.9; H, 6.2; N, 4.6. $C_{19}H_{19}NO_3$ requires: C, 73.8; H, 6.2; H, 4.5%).

4 - *Formyl* - 3 - (3,4 - *dimethoxyphenyl*) - 2 - *methylisocarbostyril* **16d**. 4-Formyl-3-(3,4-dimethoxyphenyl)-2-methyl-1,2-dihydroisoquinoline (1.5 g) in acetone (125 ml) was stirred with activated manganese dioxide (7.5 g) for 18 hr at room temperature and then filtered. The acetone filtrate was dried ($MgSO_4$) and evaporated to dryness under reduced pressure. The solid product was recrystallised from methanol as white plates m.p. 182–184° (1.34 g, 86%). ν_{max} cm^{-1}, 1678, 1650. λ_{max} nm (ϵ), 237 (17,200). ^1H NMR ($CDCl_3$): 3.35 (s, 3H, N-CH_3), 3.9 (s, 3H, -OCH_3), 4.0 (s, 3H, -OCH_3), 8.4 (m, 1H, C_8-H), 9.1 (m, 1H, C_5-H), 6.8–7.9 (complex, 5H, remaining aromatic protons), 9.55 (s, 1H, -CHO). (Found: C, 70.4; H, 5.3; N, 4.4. $C_{19}H_{17}NO_4$ requires: C, 70.6; H, 5.3; N, 4.3%).

4 - *Methoxymethylene* - 3 - (3,4 - *dimethoxyphenyl*) - 2 - *methyl* - 1,4 - *dihydroisoquinolinium tetrafluoroborate* **17a**. 4-Formyl-3-(3,4 - dimethoxyphenyl) - 2 - methyl - 1,2 - dihydroisoquinoline (300 mg) and triethyloxonium tetrafluoroborate (190 mg) were dissolved in dry dichloromethane (5 ml) and the solution was stirred for 2 hr and then left to stand for a further 16 hr, all at room temp. The solvent was then evaporated under reduced pressure to yield a brown gum, which upon trituration with ethanol yielded the ethoxy iminium ether **17b** as a yellow powder. ^1H NMR ($CDCl_3$): 1.4 (t, 3H, J = 7Hz, -CH_2-CH_3), 3.5 (s, 3H, $\overset{+}{N}$-CH_3), 4.0 (s, 6H, 2×-OCH_3), 4.25 (q, 2H, J = 7Hz, -CH_2-CH_3), 5.1 (br.s, 2H, $\overset{+}{N}$-CH_2-), 8.0 (m, 1H, C_5-H), 6.95–7.5 (complex, 7H, aromatic and olefinic protons). The ethoxy iminium ether was then recrystallised from methanol to give the methoxy ether as pale lemon prisms m.p. 210–212° (340 mg, 86%). ν_{max} cm^{-1} 1613, 1576. λ_{max} nm (ϵ), 228 (24,200), 290 (16,000), 354 (12,600). ^1H NMR (d_6-DMSO): 3.2 (s, 6H, ($\overset{+}{N}$-CH_3 and >C=C-OCH_3), 3.9 and 3.95, (2s, 6H, 2×-OCH_3), 4.95 (s, 2H, $\overset{+}{N}$-CH_2-), 8.3 (m, 1H, C_5-H), 7.1–7.85 (complex, 7H, aromatic and olefinic protons). (Found: C, 58.7; H, 5.6; N, 3.3. $C_{20}H_{22}NO_3 \cdot BF_4$ requires: C, 58.4; H, 5.4; N, 3.4%).

4 - *Methoxycyanomethyl* - 3 - (3,4 - *dimethoxyphenyl*) - 2 - *methyl* - 1,2 - *dihydroisoquinoline* **20**. KCN (0.68 g) in water (30 ml) was added to the methoxy iminium ether **17a** (2.0 g) in dichloromethane (120 ml) and the heterogeneous mixture was stirred at room temp. for 16 hr. The aqueous layer was separated and extracted with dichloromethane (2×30 ml) and these extracts were combined with the dichloromethane layer and thoroughly washed with water (5×30 ml). The dichloromethane was then dried ($MgSO_4$) and the solvent was evaporated under reduced pressure to yield a brown gum. Trituration with ether yielded the product as a white solid, which was recrystallised from methanol as white needles m.p. 142–144° (dec.) (1.47 g, 86%). ν_{max} cm^{-1}, 2240, 1610, 1594. λ_{max} nm (ϵ), 240 (12,200), 344 (7800). ^1H NMR ($CDCl_3$): 2.65 (s, 3H, N-CH_3), 3.4 (s, 3H, -CH(CN)-OCH_3), 3.9 (s, 6H, 2×-OCH_3), 4.4 (s, 2H, N-CH_2-), 4.6 (s, 1H, CH_3O-CH(CN)-), 6.8–7.6 (complex, 7H, aromatic protons). (Found: C, 72.0; H, 6.4; N, 7.9. $C_{21}H_{22}N_2O_3$ requires: C, 72.0; H, 6.3; N, 8.0%).

7,8 - *Dimethoxy-4-(3,4-dimethoxyphenylacetoyl)* - 2 - *methyl* - 1,2 - *dihydroisoquinoline* **21**. 7,8 - Dimethoxyisoquinoline methochloride (3 g) was suspended in dry ether (150 ml) and LAH (0.5 g) was added portionwise with stirring, and when addition was complete the suspension was stirred for a further 3 hr. The excess LAH was then destroyed by cautious addition of aqueous sodium potassium tartrate solution. The ether layer was run off, dried ($MgSO_4$) and placed in a separate flask containing triethylamine (1.5 g). Homoveratroyl chloride (3 g) in dry ether (100 ml) was then added dropwise over a period of 20 min to this ethereal mixture. After addition was complete the mixture was stirred for a further 3 hr and then left to sand at room temp. for 14 hr after which it was filtered. The residue was stirred with water (100 ml) for 30 min and then filtered again. The undissolved solid product was recrystallised from methanol as white plates m.p. 110–112° (2.6 g, 55%). ν_{max} cm^{-1}, 1615. λ_{max} nm (ϵ), 220 (13,200), 289 (9800), 355 (5300). ^1H NMR ($CDCl_3$): 3.0 (s, 3H, N-CH_3), 3.9 (complex, 12H, 4×-OCH_3), 4.5 (s, 2H, N-CH_2), 8.4 (d, 1H, J = 9Hz, C_5-H), 6.7–8.4 (complex, 5H, remaining aromatic protons). (Found: C, 69.4; H, 6.5; N, 3.7. $C_{22}H_{25}NO_5$ requires: C, 68.9; H, 6.6; N, 3.7%).

7,8 - *Dimethoxy* - 4 - *ethoxy(3',4'-dimethoxybenzyl)* - *methylene* - 2 - *methyl* - 1,4 - *dihydroisoquinolinium tetrafluoroborate* **22**. The acylated enamine **21** (380 mg) and triethyloxonium tetrafluoroborate (190 mg) were dissolved in dry dichloromethane (5 ml) and the solution was stirred for 2 hr and then left to sand for a further 16 hr. The solvent was then evaporated under reduced pressure to yield a yellow gum, which upon trituration was ethanol yielded the ethoxy iminium ether **22** m.p. 160–162° (390 mg, 78%). ν_{max} cm^{-1}, 1659. λ_{max} nm (ϵ), 224 (16,800), 282 (13,400), 360 (6000). ^1H NMR ($CDCl_3$): 1.5 (t, 3H, J = 7Hz, -CH_2-CH_3), 3.6 (s, 3H, $\overset{+}{N}$-CH_3), 3.95 (m, 12H, 4×-OCH_3), 4.35 (s, 2H, Ar-CH_2-), 4.4 (q, 2H, J = 7Hz, CH_3-CH_2-), 8.1 (d, 1H, J = 9Hz, C_5-H), 8.6 (s, 1H, C_3-H), 6.7–7.1 (complex, 4H, remaining aromatic protons). (Found: C, 57.3; H, 5.7; N, 2.8. $C_{24}H_{30}NO_5 \cdot BF_4$ requires: C, 57.7; H, 6.0; N, 2.8%).

Attempted ring closures of the iminium salt **22**. The iminium salt **22** (250 mg) was heated under reflux in ethanol (25 ml) for 1 hr and allowed to cool. The precipitated solid proved to be 7,8 - dimethoxy - 4 - (3,4 - dimethoxyphenylacetoyl) - 2 - methylisoquinolinium tetrafluoroborate **23** m.p. 168–169°. ν_{max} cm^{-1}, 1698. λ_{max} nm (ϵ), 275 (15,500), 336 (6400). ^1H NMR (d_6 DMSO): 3.8 (s, 6H, 2×-OCH_3), 4.1 (s, 6H, 2×-OCH_3), 4.5 (s, 2H, Ar-CH_2-), 4.6 (s, 3H, $\overset{+}{N}$-CH_3), 7.0 (complex, 3H, aromatic protons), 8.2 (s, 2H, aromatic protons), 9.2 (s, 1H, C_3-H), 10.0 (s, 1H, C_1-H). (Found: C, 56.5; H, 5.1; N, 2.8. $C_{22}H_{24}NO_5 \cdot BF_4$ requires: C, 56.3; H, 5.2; C, 3.0%).

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