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The Electrochemical Oxidation of Aromatic Ethers. Part 12[1]
The anodic oxidation of 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolin-3(2-H)-one and attempts to synthesise 2-acyl-4-benzyl-1,2,3,4-tetrahydroisoquinolines through the C-4 alkylation of tricarbonyl η^6-1,2,3,4-tetrahydroisoquinoline chromium (0) complexes

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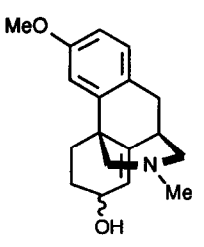
Abstract: We have reinvestigated the anodic oxidation of 1,4-dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolin-3(2H)-one and found it to yield a new product: 2,3,7,9-tetramethoxy-11-(N-methylacetamido)dibenzo[*a*,*e*]cycloheptatrien-5-one. In order to investigate reactions of this type 2-acyl-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-1,2,3,4-tetrahydroisoquinolines were required. Attempts to synthesise these compounds from the chromium tricarbonyl complexes of 2-acyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines have failed, leading instead to 2-acyl-1,4-dibenzyl-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinolines

Isomorphinans in which the nitrogen atom is at position 15, rather than at 14 as it is in the morphinans, are represented by compound (1) which has analgesic, antibacterial, and antifungal activity[2]. There are few other examples of this type of tetracyclic system[3] and we have sought extend the list by synthesising the derivative (2), through the anodic oxidation of the 4-benzyl-1,2,3,4-tetrahydroisoquinolinone (3). Unfortunately this reaction failed giving instead a number of products, including the dehydrodimer (4) and the trione (5)[4]. The last compound arises through over-oxidation and in new work we have repeated this coupling reaction under more carefully controlled conditions than used previously and at higher dilution (to minimise dehydrodimer formation), but, the required isomorphinan still eludes us. The only product obtained was the tricycle (7) which we assume forms *via* the intermediacy of the tetracycle (6).

The reasons for the variation in products from reaction to reaction are unclear, but we have circumstantial evidence that the desired coupling reaction between C-6 of the benzyl substituent and C-8a of the isoquinoline nucleus does occur in the electrochemical oxidations of *N*-acyl-1,2,3,4-tetrahydroisoquinolines (8, R=CHO, Ac, or CF_3CO). These yielded the phenanthrene (9)[4], and we suggest that the intermediate cations, or their equivalents, undergo preliminary *N*-deacylation before further oxidation. Should this be the case we considered that a bulky amido substituent might be advantageous, acting to disfavour nucleophilic attack at the carbonyl group. Thus we decided to examine the anodic oxidation of the *N*-pivaloyl derivative (13, R=OMe); we also wished to examine the electrochemistry of the 4-benzyl-1,2,3,4-tetrahydroisoquinoline (13, R=H) bearing only two methoxy groups, one in each benzenoid ring *para* to the desired sites for

coupling. This should reduce the possibility of dehydrodimerisation and also rearrangement, such as that noted during the anodic cyclisation of the isochromanone (11) to the spiro compound (12) - a reaction mediated by the presence of the methoxy group at C-7[4].



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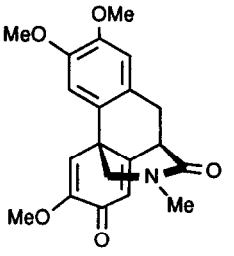

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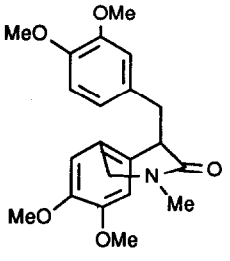

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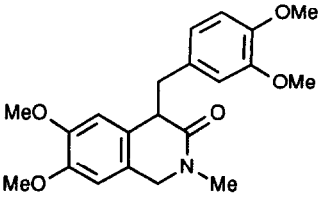

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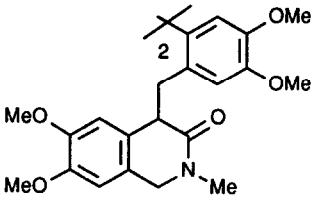

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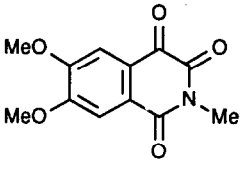

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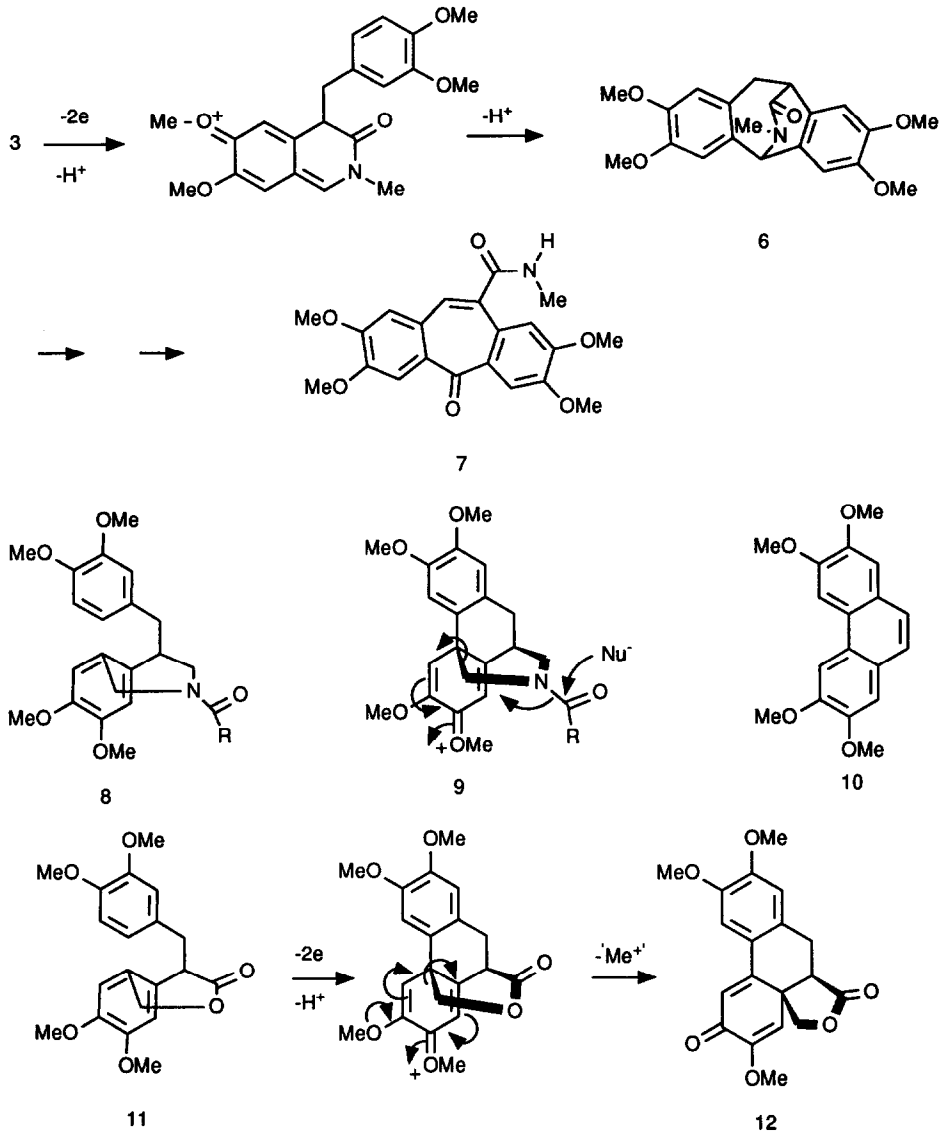
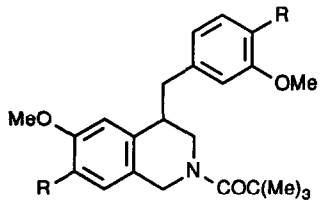


Rather than use traditional routes to these two *N*-acyltetrahydroisoquinolines[5] we sought to synthesise them by the direct C-4 alkylation of the simple isoquinolines (14, R=^{1}R=OMe) and (14, ^{1}R=OMe, R=H) respectively. Tricarbonyl-η^6-[2-methyl-1,2,3,4,-tetrahydroisoquinoline chromium] (0) can be deprotonated at C-4 by ^{n}butyl lithium and the corresponding anion successfully reacted at this site with electrophiles. Davies[6] suggests that the regioselectivity is caused by initial complexation of the base with the pseudo axially



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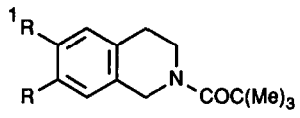

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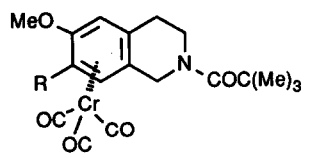
orientated lone pair electrons on the nitrogen atom of the isoquinoline ring, followed by abstraction of the proximal C-4 axial proton. However, in the complexes (15) resonance in the amide group should disfavour this reaction, and Beak has shown[7] that the deprotonation of uncomplexed *N*-acyl-1,2,3,4-tetrahydroisoquinolines with ^{n}butyl lithium occurs exclusively at C-1, through chelation control. Neither Davies nor Beak have examined methoxylated derivatives in this series, and we speculated that resonance involving the 6-methoxy group in our tetrahydroisoquinoline complexes (see 16) might destabilise carbanion formation at C-1 enough to redirect deprotonation to C-4.

In practice this proved incorrect and deprotonation of the complex (15, R=H), reaction with 3-methoxybenzyl chloride, and decomplexation, gave the 1-benzyl derivative (17, R=H). Similarly the dimethoxylated complex (15, R=OMe) was deprotonated and reacted with a series of electrophiles to give the corresponding 1-substituted complexes (see 18). We noted, however, that if the 1-benzylated complex (18, R=CH_2Ph) was treated with potassium hexamethyldisilazide (KHDMS) and a second equivalent of benzyl bromide the 1,4-dibenzyl complex (19 R=CH_2Ph)) was formed. An similar reaction occurred between the 1-propyl complex (18, R=C_3H_7), ^{n}butyl lithium and propyl iodide affording the 1,4-dipropyl compound (19, R=C_3H_7).

Clearly, if the C-1 substituent could be easily removed this technique could be adapted for the synthesis of 4-substituted isoquinolines and it was for this reason that the trimethylsilyl complex [18, R=Si(Me)$_3$] was prepared. Treatment of this with equimolar amounts of ^{n}butyl lithium and benzyl bromide gave 33% unchanged starting material and 22% of the complex (15, R=OMe). Presumably the TMS group is displaced by the base, however, if this is so we are unable to explain why no C-benzylated product was isolated since this should generate the carbanion at C-1. We reasoned that a more hindered base might disfavour nucleophilic attack at silicon, but although treatment of [18, R=Si(Me)$_3$] with LiHDMS yielded a yellow precipitate, indicative of carbanion formation, addition of benzyl bromide gave no new products. Treatment of the silylated complex with KHDMS and benzyl bromide was equally unproductive. Widdowson has shown that although the TMS group is easily displaced from the chromium tricarbonyl complex of 2-methyl-5-trimethylsilylthiophene by reaction with ^{t}butyl lithium, the ^{t}butyldimethylsilyl analogue is much more stable and reaction with the base leads to deprotonation at C-4[8]. All attempts to introduce a TBDMS group at C-1 into our complex (15, R=OMe) failed.

Another easily removable group is hydroxybenzyl and we noted that when the complex [18, R=CH(OH)Ph] was treated with KHDMS a salt formed, which when allowed to warm to room temperature underwent a retro aldol reaction (see 20) to return the complex (15, R=OMe). The corresponding lithium salt is much more

stable and survives for several hours at this temperature, perhaps because of enhanced chelation between the metal and the amide carbonyl group.



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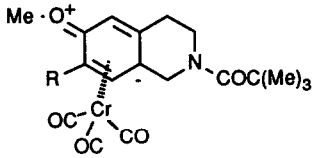

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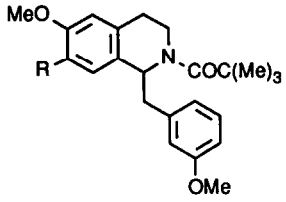

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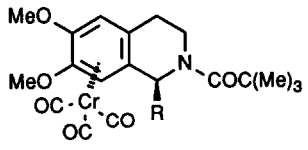

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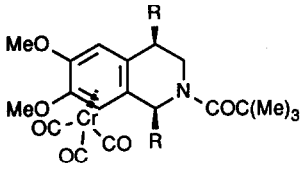
R= CH_2Ph
R= CH(OH)Ph
R= COPh
R= C_3H_7
R= $CH_2CH{=}CH_2$
R= $Si(Me)_3$



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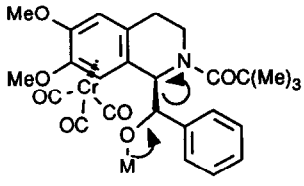

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When the complex [18, R=CH(OH)Ph] was treated with two equivalents of KHDMS and two equivalents of 3-methoxybenzyl chloride at -78 C and then allowed to warm to -25° C a new product formed, this was treated with acid and decomplexed to afford 1-(3-methoxybenzyl)-6,7-dimethoxy-1,2,3,4-tetrahydroisoquinoline (17, R=OMe).

Since we know that KHDMS is sufficiently basic to effect deprotonation at C-4 in the 1-benzylated complex [18, R=CH_2Ph] the question arises, if such an anion is formed here why does it not react with the available electrophile? The ^1H NMR spectrum of the complex [18, R=CH(OH)Ph] shows the presence of two diastereomers in the ratio 9:1. In the spectrum of the major isomer the C-4 proton resonances occur at 2.55 and 2.22 ppm, and those of C-3 at 3.87 ppm. By comparison the relevant signals for the C-1 benzylated complex [18, R=CH_2Ph] occur at 2.55 and 2.65 ppm, and 3.55 4.00 ppm respectively. Such changes in chemical shifts signify that the phenyl group of the complex is orientated over the top of the piperidine ring and may hinder the approach of the electrophile. Should this be the case then a smaller group at C-1 may be

helpful and studies of this type are included in our future plans.

EXPERIMENTAL

All manipulations involving tricarbonyl-η^6-arene chromium (0) complexes were performed using deoxygenated solvents. Infra-red spectra were recorded on a Perkin-Elmer 983G spectrometer, as Nujol mulls. ^{1}H N.M.R. spectra were recorded on Bruker ACE 200 (200 MHz) or Bruker AMX 400 (400 MHz) spectrometers in $CDCl_3$ unless otherwise stated. Mass spectra were recorded on a V.G. 7070E spectrometer (CI spectra were generated using ^{i}butane). TLC analyses were conducted using Merck Silica Gel 60 F_{254} plates.

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolin-3(2H)-one (3)

Lithium hexamethyldisilazide (1.0 M in THF; 10.9 cm^3, 10.9 mmol) was added dropwise to a stirred solution of 1,4-dihydro-6,7-dimethoxyisoquinolin-3(2H)-one (2.0g, 9.05 mmol) in THF (30 cm^3) at -70°C, under argon. After 1h a solution of 3,4-dimethoxybenzyl chloride (2.03 g, 10.9 mmol) in THF (5cm^3) was added to the orange solution, and after a further 1h, the solution was poured into saturated aqueous NH_4Cl (200 cm^3). The mixture was extracted with dichloromethane (2 x 100 cm^3), and the combined extracts washed with brine (100 cm^3) dried ($MgSO_4$) and evaporated under reduced pressure to leave a yellow gum. This was purified by column chromatography over silica, eluting with ethyl acetate to give a colourless gum (1.2g, 36%); υ_{max}, (cm^{-1}) 1630; δ_H (400 MHz) 6.63 (1H, d, J = 8.2 Hz, 5′-H), 6.46 and 6.44 (2H, 2 x s, 5-H and 8-H), 6.31 (1H, dd, J = 8.2, 2.0 Hz, 6′-H), 6.23 (1H, d, J = 2.0 Hz, 2′-H), 3.87-3.79 (2H, obscured, 1-H and 4-H), 3.84 (3H, s. OMe), 3.83 (3H, s, OMe), 3.82 (3H, s, OMe), 3.64 (3H, s, OMe), 3.42 (1H, d, J = 15.5 Hz, 1-H), 3.23 (1H, dd, J = 13.0, 6.1 Hz, CHC$\underline{H}_2$Ar), 2.99 (1H, dd, J = 13.0, 4.1 Hz CHC$\underline{H}_2$Ar), 2.95 (3H, s, NMe) [Found: *m/z* 371.17331 calculated for $C_{21}H_{25}NO_5$: 371.17327].

2,3,7,8-Tetramethoxy-11-(N-methylacetamido)dibenzo[a,e]cycloheptatrien-5-one (7)

1,4-Dihydro-6,7-dimethoxy-4-(3,4-dimethoxybenzyl)-2-methylisoquinolin-3(2 H)-one[1] (3) (0.60g, 1.6 mmol) was dissolved in dry acetonitrile (100 cm^3) containing anhydrous sodium perchlorate, and the solution placed in a single compartment cell, under argon. Current was passed through the solution at an anode potential of +1.2V (vs. SCE) using platinum electrodes until 2F mol^{-1} of electrons had been consumed. The dark brown solution was reduced in volume, water (20 cm^3) added and the mixture extracted with ethyl acetate (3 x 50 cm^3). The combined ethyl acetate extracts were dried ($MgSO_4$) and evaporated under reduced pressure to leave a dark brown solid, which was subjected to column chromatography over silica, eluting with ethyl acetate, to give the title compound (7), (14 mg), m.p. 254-256°C (methanol): υ_{max} (cm^{-1}) 3280, 1635, 1620; δ_H (d^6-DMSO) 8.50 (1H, q, J = 4.7 Hz, NH), 8.05 and 8.00 (2H, 2 x s 4-H and 6-H), 7.80 and 7.78 (2H, 2 x s, 1-H and 9-H), 7.45 (1H, s, 10-H), 4.04 (6H, s, 2 x OMe), 3.90 (3H, s, OMe), 3.84 (3H, s, OMe), 2.87 (3H, m, $NHCH_3$); *m/z* (E.I.) 355 (M^+-28, 100%), 325 (50%), 131 (40%); C.I. 356 (M^++ 1 (-28), 100%). Starting material (138mg) was recovered from later fractions.

1,2,3,4-Tetrahydro-6-methoxy-2-pivaloylisoquinoline (14, R′=OMe; R=H)

A solution of 1,2,3,4-tetrahydro-6-methoxyisoquinoline[9] (8.2 g, 50 mmol) and triethylamine (10.12 g, 100 mmol) in dry chloroform (50 cm^3) was added to a water-cooled, stirred solution of pivaloyl chloride (6.03 g, 50 mmol) in dry chloroform (50 cm^3). After 17h, the reaction was washed with water (2 x 25 cm^3), the chloroform dried ($MgSO_4$) and evaporated under reduced pressure to leave a pale yellow waxy solid (11.3 g) which was purified by column chromatography over alumina, eluting with diethyl ether, to give colourless crystals (10.0g, 81%), m.p. 60.5-62°C (hexane): υ_{max} (cm^{-1}) 1640, 1610; δ_H 7.00 (1H, d, J = 8.5 Hz, 8-H), 6.73 (1H, dd, J = 8.5, 3.0 Hz, 7-H), 6.64 (1H, d, J = 3.0 Hz, 5-H), 4.67 (2H, s, 1-H), 3.81 (2H, t, J = 5.9 Hz, 3-H), 3.76 (3H, s, OMe), 2.83 (2H, t, J = 5.9 Hz, 4-H), 1.30 (9H, s, t-Bu) [Found: C, 72.7; H, 8.8; N, 5.7. $C_{15}H_{21}NO_2$ requires C, 72.8; H, 8.55; N, 5.7%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6-methoxy-2-pivaloylisoquinoline chromium] (0) (15, R=H)

A stirred mixture of 1,2,3,4-tetrahydro-6-methoxy-2-pivaloylisoquinoline (5.76 g, 23.3 mmol) and hexacarbonylchromium (0) (5.63 g, 25.6 mmol) in 10% tetrahydrofuran/di-^{n}butyl ether (40 cm^3) was heated to reflux, under nitrogen, for 30h. The green mixture was diluted with ethyl acetate, filtered, evaporated under reduced pressure and the green residue purified by column chromatography, over silica, eluting with ethyl acetate, to give a yellow gum (8.5g). The gum was crystallised by adding diethyl ester (150 cm^3) and then slowly adding dichloromethane until a solution formed. Evaporation of the solvents, under reduced pressure, resulted in the precipitation of yellow crystals. A small volume of diethyl ether was added and the crystals filtered (6.14 g, 69%), m.p. 148-149°C: υ_{max} (cm^{-1}) 1950, 1875, 1860, 1620; δ_H 5.50 (1H, d, J = 7.3 Hz, 8-H), 5.20 (1H, dd, J = 7.3, 2.0 Hz, 7-H), 5.02 (1H, d, J = 2.0 Hz, 5-H), 4.88 (1H, d, J = 16.7 Hz, 1-H), 4.21 (1H, dt, J = 14.0, 5.0 Hz, 3-H), 4.09 (1H, d, J = 16.7 Hz, 1-H), 3.7 (3H, s, OMe), 3.58 (1H, ddd, J = 14.0, 10.0, 5.0 Hz, 3-H), 2.9 (1H, ddd, J = 14.0, 10.0, 5.0 Hz, 4-H), 2.7 (1H, dt, J 14.0, 5.0 Hz, 4-H), 1.31 (9H, s, t-Bu)[Found: C, 56.9; H, 5.6; N, 3.9 $C_{18}H_{21}NO_5$ requires C, 56.4; H, 5.5; N, 3.65%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6-methoxy-1-(3-methoxybenzyl)-2-(2,2-dimethyl-1-oxopropyl)isoquinoline chromium] (0)

^{n}Butyllithium (1.6M in hexanes; 0.81 cm^3, 1.43 mmol) was added dropwise to a well-stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6-methoxy-2-pivaloylisoquinoline] chromium (0) (15, R=H) (0.5 g, 1.3 mmol) in THF (5 cm^3) at 70°C, under argon. After 1h, 3-methoxybenzyl chloride (0.22 g, 1.43 mmol) was added to the orange solution and stirring was continued for 1h. The solution was allowed to warm to room temperature, the solvent was evaporated under reduced pressure and the solid purified by column chromatography, on silica, eluting with ethyl acetate, giving a yellow solid, which crystallised from the column fractions (0.17 g, 25%), m.p. 187-188°C (dec.): δ_H 7.20 (1H, t, J = 7.0, 5′-H), 6.79 (1H, d, J = 7.0 Hz, 4′-H), 6.70 (2H, m, 2′-H and 6′-H), 5.37 (1H, br m, 1-H), 5.06 (1H, s, 5-H), 5.0 (1H, d, J = 7.0 Hz, 8-H), 4.87 (1H, d, J = 7.0 Hz, 7-H), 4.20 (1H, br m, 3-H), 3.80 (3H, s, OMe), 3.70 (3H, s, OMe), 3.45 (1H, m, 3-H), 3.1-2.95 (3H, m, PhC$\underline{H}_2$ and 4-H), 2.59 (1H, dt, J = 14.7 Hz, 4-H), 1.3 (9H, s, t-Bu)[Found: C, 61.95; H, 5.8; N, 2.8 $C_{27}H_{29}CrNO_6$ requires C, 62.9; H, 5.7; N, 2.7%].

1,2,3,4-Tetrahydro-6-methoxy-1-(3-methoxybenzyl)-2-pivaloylisoquinoline (17, R=H)

A solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6-methoxy-1-(3-methoxybenzyl)-2-pivaloylisoquinoline chromium] (0) (25 mg, 49.3 μmol) in ethyl acetate (20 cm^3) was exposed to air and sunlight for 18h. The brown mixture was filtered through a short silica column and the solvents evaporated under reduced pressure, to give a colourless gum (15.5 mg, 86%): $\upsilon_{(max)}$ (cm^{-1}) 1620; δ_H 7.14 (1H, t, J = 6.8 Hz, 5'-H), 6.80 (1H, d, J = 8.3Hz, 6'-H), 6.76-6.63 (5H, m, 5-H, 7-H, 8-H, 2'-H and 4'-H), 5.77 (1H, br m, 1-H), 4.14 (1H, br m, 3-H), 3.78 (3H, s, OMe), 3.74 (3H, s, OMe), 3.33 (1H, ddd, J = 13.7, 11.7, 4.0 Hz, 3-H), 3.09 and 3.08 (2H, 2 x s, $PhCH_2$), 2.91 (1H, ddd, J = 16.5, 11.7, 5.7 Hz, 4-H), 2.67 (1H, dt, J = 16.5, 6.4, 4.0 Hz, 4-H), 1.23 (9H, s, t-Bu); *m/z*(C.I.) M^++ 1 368 (100%), 246 (70%).

1,2,3,4-Tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline (14, R=R=OMe)

Triethylamine (23 cm^3, 163 mmol) was added to a stirred suspension of 1,2,3,4-tetrahydro-6,7-dimethoxy-isoquinoline hydrochloride (12.5 g, 54.4 mmol) in chloroform (125 cm^3), cooled in an ice-water bath. After 10 min, a solution of pivaloyl chloride (7.2 g, 59.8 mmol) in chloroform was added dropwise. The clear solution was stirred for 0.5 h then washed with hydrochloric acid (2M; 100 cm^3), water 100 cm^3), sodium bicarbonate solution (100 cm^3), then dried ($MgSO_4$). The solvent was evaporated under reduced pressure to give a colourless solid (15.2g), which was crystallised from di-isopropylether (12.2 g, 81%), m.p. 122-124°C; υ_{max} (cm^{-1}) 1615; δ_H 6.62 and 6.60 (2H, 2 x s, 5-H and 8-H), 4.68 (2H, s, 1-H), 3.86 (6H, s, 2 x OMe), 3.84 (2H, t, J = 6.7 Hz, 3-H), 2.81 (2H, t, J = 6.7 Hz, 4-H), 1.32 (9H, s, t-Bu) [Found: C, 69.2; H, 8.4; N, 5.1 $C_{16}H_{23}NO_3$ requires C, 69.3; H, 8.35; N, 5.05%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinolinechromium] (0 (15, R=OMe)

A suspension of 1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline (11.08 g, 40 mmol) and hexacarbonyl chromium (0) (9.24 g, 42 mmol) in 10% THF/di-^{n}butylether (250 cm^3) was heated to reflux, under nitrogen, for 42 h, then cooled and filtered. The solid obtained was washed with a small volume of hexane and dried. A solution of the solid (13.1 g) in dichloromethane was filtered through a short pad of Florisil, the filtrate concentrated to approximately 50-60 cm^3 then di-isopropylether (350 cm^3) added. This caused a yellow solid to separate which was collected, washed with di-isopropylether, and dried under reduced pressure (11.0 g, 67%), m.p. 186.5-187°C (dec.): υ_{max} (cm^{-1}) 1950, 1875, 1855, 1620: δ_H 5.23 and 5.22 (2H, 2 x s, 5-H and 8-H), 4.94 (1H, d, = 16.7 Hz, 1-H), 4.31 (1H, dt, J = 13.3, 3.3 Hz, 3-H), 4.15 (1H, d, J = 16.7 Hz, 1-H), 3.80 (3H, s, OMe), 3.78 (3H, s, OMe), 3.35 (1H, ddd, J = 13.3, 10.0, 3.3 Hz, 3-H), 2.78 (1H, ddd, J = 16.7, 10.0, 6.0 Hz, 4-H), 2.51 (1H, dt, J = 16.7, 3.3 Hz, 4-H), 1.31 (9H, s, t-Bu)[Found : C, 55.3; H, 5.7; N, 3.1 $C_{19}H_{23}CrNO_6$ requires C, 55.2; H, 5.6; N, 3.4%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-1-benzyl-6,7-dimethoxy-2-pivaloylisoquinolinechromium] (0)
(18, R=CH_2Ph)

^{n}Butyllithium (1.49 M in hexanes; 0.62 cm^3 0.93 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (0.31 g, 0.75 mmol)

in THF (7 cm^3) cooled to 65°C, under nitrogen. After standing for 0.5h a yellow precipitate separated from the orange coloured solution, and after a further 1.5 h, this suspension was warmed to -30°C. The resulting orange solution was added to a stirred solution of benzyl bromide (freshly distilled from CaH)(0.13 g, 0.75 mmol) in THF (1.0 cm^3) at -65°C. After 0.5 h, the solution was warmed to room temperature, the solvent removed under reduced pressure and the residue (0.5 g) purified by column chromatography on silica, eluting with 7:13 ethyl acetate/hexane, giving a yellow solid (0.3 g, 80%), m.p. 165-167°C (dec.): δ_H (400 MHz) 7.35-7.1 (5H, m, ArH, 5.32 (1H, partially obscured dd, J = 10.0, 5.3 Hz, 1-H), 5.28 (1H, s, 5-H), 4.37 (1H, s, 8-H), (3H, s, OMe), 4.06-3.94 (1H, m, 3-H), 3.80-3.62 (1H, m, 3-H), 3.33 (3H, s, OMe), 3.25 (1H, dd, J = 12.7, 5.3 Hz, 4-H), 2.85 (1H, dd, J = 12.7, 10.0 Hz, 4-H), 2.78-2.63 (1H, m, PhCH), 2.50 (1H, dt, J = 16.0, 6.0 Hz, PhCH), 1.33 (9H, s, t-Bu)[δ_H (400 MHz) (d^6-DMSO) 7.3-7.16 (5H, m, Ph), 5.95 and 5.85 (2H, 2 x s, 5-H and 8-H), 5.50 (1H, t, J = 7.0 Hz, 1-H), 4.00 (1H, m, 3-H), 3.75 (3H, s, OMe), 3.60 (3H, s, OMe), 3.60 (1H, obscured m, 3-H), 3.20 (1H, dd, J = 16.0, 7.0 Hz, PhCH), 3.03 (1H, dd, J = 16.0, 10 Hz, PhCH), 2.65 (1H, m, 4-H), 2.55 (1H, br d, obscured by DMSO, J = 16 Hz), 1.05 (9H, s, t-Bu)][Found: C, 62.2; H, 6.0; N, 2.8 $C_{26}H_{29}CrNO_6$ requires C, 61.9; H, 5.8; N, 2.8%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-1-(hydroxyphenylmethyl)-6,7-dimethoxy-2-pivaloylisoquinoline]-chromium (0) [18, R=CH(OH)Ph]

^{n}Butyllithium (1.6 M in hexanes; 1.66 cm^3, 2.66 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (1.0 g, 2.42 mmol) in THF (75 cm^3) cooled to 65°C, under argon. After 0.5 h the solution was warmed to -20°C and after a further 10 min, benzaldehyde (0.27 cm^3, 2.66 mmol) was added rapidly. Stirring was continued for 1 h, then acetic acid (0.5 cm^3) was added and the cloudy solution allowed to warm to room temperature. The solvents were evaporated under reduced pressure and the residue partitioned between water (50 cm^3) and dichloromethane (100 cm^3). The aqueous phase was extracted with more dichloromethane (50 cm^3) and the combined extracts dried ($MgSO_4$) and evaporated to leave a yellow solid (1.3g). Ethyl acetate (100 cm^3) was added and the solid filtered (0.55 g, 44%), m.p. 193-194°C (dec.). Major isomer: υ_{max} (cm^{-1}) 3320, 1950, 1875, 1850, 1610; δ_H (400 MHz; d^6-DMSO) 7.20 (5H, m, Ph), 6.10 and 5.90 (2H, 2 x s, 5-H and 8-H), 5.61 (1H, d, J = 4.2 Hz, OH), 5.51 (1H, m, 1-H), 5.16 (1H, t, J = 4.2 Hz, PhCHOH), 3.87 (2H, m, 3-H), 3.74 (3H, s, OMe), 3.60 (3H, s, OMe), 2.55 (1H, obscured m, 4-H), 2.12 (1H, br d, J = 16.2 Hz, 4-H), 1.06 (9H, s, t-Bu). Minor isomer: δ_H (400 MHz; d^6-DMSO) 6.00 (1H, s), 5.72 (1H, s), 5.35 (1H, s), 5.30 (1H, d, J = 4 Hz), 4.90 (1H, m), 1.78 (1H, m) [Found : C, 58.9; H, 5.6; N, 2.6 $C_{26}H_{29}CrNO_7$ requires C, 60.1; H, 5.6; N, 2.7%].

Tricarbonyl-η^6-[1-benzoyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (18, R=COPh)

^{n}Butyllithium (1.49 M in hexanes; 0.62 cm^3, 0.93 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (0.31 g, 0.75 mmol) in THF (7.0 cm^3) cooled to -65°C, under nitrogen. The orange solution deposited a yellow precipitate after 0.5 h and, after a further 2 h, the suspension was warmed to -30°C. The resulting solution was added to a stirred

solution of benzoyl chloride (freshly distilled; 0.11 g, 0.75 mmol) in THF (1.0 cm^3) at -65°C. After 10 min, the solution was warmed to room temperature, the solvent removed under reduced pressure and the residue (0.52 g) purified by column chromatography on silica, eluting with 35:65 ethyl acetate/hexane, giving a yellow solid (0.2g, 55%), m.p. 157.5-158°C (dec.): υ_{max} (cm^{-1}) 1965, 1875, 1865, 1675, 1640; δ_H 8.10-8.05 (2H, m, 2′-H, 6′-H), 7.66-7.45 (3H, m, 3′-H, 4′-H, 5′-H), 6.26 (1H, s, 1-H), 5.30 and 4.90 (2H, s, 5-H and 8-H), 4.20 (1H, dt, J = 12.7, 5.3 Hz, 3-H), 3.77 (3H, s, OMe), 3.72-3.69 (1H, m, 3-H), 3.47 (3H, s, OMe), 3.05 (1H, ddd, J =14.7, 8.7, 5.3 Hz, 4-H), 2.53 (1H, dt, J = 14.7, 5.3 Hz, 4-H), 1.31 (9H, s, t-Bu)[Found : C, 60.3; H, 5.3; H, 2.65. $C_{26}H_{27}CrNO_7$ requires C, 60.35; H, 5.3; N, 2.7%].

Tricarbonyl-η^6-[-1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloyl-1-(1-propyl)isoquinoline] chromium (0) (18, R=Pr)

^{n}Butyllithium (1.49 M in hexanes; 0.31 cm^3, 0.46 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (0.15 g, 0.75 mmol) in THF (3.5 cm^3) cooled to -65°C, under nitrogen. The orange solution deposited a yellow precipitate after 0.5 h and, after a further 1.5 h, the suspension was warmed to -30°C. The resulting solution was added to a stirred solution of 1-iodopropane (0.065g, 0.75 mmol) in THF (0.5 cm^3) at -65°C. After 10 min, the solution was warmed to room temperature during 18h. The solvent was removed under reduced pressure and the residue (0.3g) purified by column chromatography on silica, eluting with 2:3 ethyl acetate/hexane, giving a yellow solid (0.1g, 55%), m.p. 163.5-164.5: υ_{max} (cm^{-1}) 1950, 1875, 1860, 1620; δ_H 5.40 (1H, dd, J = 7.3, 6.6 Hz, 1-H), 5.26 (1H, s, Ar-H), 5.20 (1H, s, Ar-H), 4.15 (1H, ddd, J = 15.0, 6.7, 3.3 Hz, 3-H), 3.80 (3H, s, OMe), 3.79 (3H, s, OMe), 3.49 (1H, ddd, J = 15.0, 10.0, 6.0 Hz, 3-H), 2.90 (1H, ddd, J = 16.7, 10.0, 6.7 Hz, 4-H), 2.59 (1H, ddd, J = 16.7, 6.0, 3.3 Hz, 4-H), 1.40-1.19 (4H, m), 1.32 (9H, s, t-Bu), 0.93 (3H, t, J = 6.7 Hz, $CH_2\underline{CH_3}$)[Found: C, 58.3; H, 6.5; N, 3.0 $C_{22}H_{29}CrNO_6$ requires C, 58.0; H, 6.4; N, 3.1%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloyl-1-(prop-3-enyl)isoquinoline] chromium (0) (18, R=$CH_2CH=CH_2$)

^{n}Butyllithium (1.49 M in hexanes; 0.62 cm^3, 0.93 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (0.31 g, 0.75 mmol) in THF (7.0 cm^3) cooled to -65°C, under nitrogen. The orange solution gave a yellow precipitate after 0.5 h and after a further 1.5 h the suspension was warmed to -30°C. The resulting orange solution was added to a stirred solution of 1-chloroprop-2-ene (86 mg, 1.125 mmol) in THF (1.0 cm^3) at -65°C. After 0.5 h, the solution was warmed to room temperature, the solvent removed under reduced pressure, and the residue (0.40 g) purified by column chromatography on silica, eluting with 2:3 ethyl acetate/hexane, giving a yellow solid (0.19 g, 56%), m.p. 173-174°C (dec.): υ_{max} (cm^{-1}) 1950, 1880, 1870, 1640, 1615; δ_H 5.85 (1H, m, $CH_2\underline{CH}=CH_2$), 5.39 (1H, t, J = 6.7 Hz, 1-H), 5.3 (1H, s, ArH), 5.2 (1H, s, ArH), 5.09 (1H, d, J = 6.9 Hz, $CH_2CH=\underline{CH}$ (Z)), 5.01 (1H, d, J = 16.7 Hz, $CH_2CH=\underline{CH}$(E)), 4.10 (1H, ddd, J = 14.7, 10.0, 6.0 Hz, 3-H), 3.80 (3H, s, OMe), 3.77 (3H, s, OMe), 3.52 (1H, ddd, J = 16.7, 10.0, 6.7 Hz, 4-H), 2.68-2.50 (3H, m, 4-H + $C\underline{H_2}CH=CH_2$), 1.30 (9H, s, t-Bu)[Found: C, 58.6; H, 6.1; N, 3.0 $C_{22}H_{27}CrNO_6$ requires C, 58.3; H, 6.0; N,

3.1%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloyl-1-trimethylsilylisoquinoline] chromium (0) [18, R=$Si(Me)_3$]

^{n}Butyllithium (1.6 M in hexanes; 1.03 cm^3, 1.64 mmol) was added dropwise to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline)]chromium (0) (0.62 g, 1.5 mmol) in THF (10 cm^3) at -70°C, under argon. After 0.5 h, the suspension was warmed to 0°C and added rapidly to a stirred solution of trimethylsilylchloride (0.2g, 1.8 mmol) in THF (2.5 cm^3) at -70°C. Stirring was continued for 1 h, then the solution was warmed to room temperature and the solvent evaporated under reduced pressure. The residue was purified by column chromatography, on silica, eluting with 3:7 ethyl acetate, giving a yellow solid (0.4 g, 55%), m.p. 168-170°C (dec.): υ_{max} (cm^{-1}) 1950, 1875, 1860, 1610; δ_H 5.29 and 4.99 (2H, 2 x s, 5-H and 8-H), 4.91 (1H, s, 1-H), 4.1-3.9 (1H, m, 3-H), 3.73 (3H, s, OMe), 3.71 (3H, s, OMe), 3.60-3.41 (1H, m, 3-H), 2.80-2.60 (1H, m, 4-H), 2.45 (1H, dt, J = 16, 6 Hz, 4-H), 1.24 (9H, s, t-Bu), 0.10 (9H, s, $SiMe_3$)[Found: C, 54.6; H, 6.5; N, 2.7 $C_{22}H_{31}CrNO_6Si$ requires: C, 54.4; H, 6.4; N, 2.9%].

Tricarbonyl-η^6-[1,4-di-(benzyl)-1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (19, R=CH_2Ph)

Potassium hexamethyldisilazide (0.5 M in toluene; 0.88cm^3, 0.44 mmol) was added to a stirred suspension of tricarbonyl-η^6-[1-benzyl-1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloylisoquinoline] chromium (0) (200 mg, 0.4 mmol) in THF (2 cm^3), at -78°C, under an atmosphere of argon. After 1h, benzyl bromide (0.53cm^3) was added, and after a further 1h, the solvent was evaporated under reduced pressure and the residue purified by column chromatography on silica, eluting with 5:1 hexane/ethyl acetate. This gave a yellow solid (134 mg, 56.5%) (76 mg of which crystallised from the column fractions), m.p. 195.5-196°C (dec.): υ_{max} (cm^{-1}) 1945, 1865, 1840, 1640; δ_H 7.40-7.10 (10H, m, 2 x Ph), 5.32 (1H, dd, J = 10, 6 Hz, 1-H), 5.13 and 4.31 (2H, 2 x s, 5-H and 8-H), 3.92 (1H, dd, J = 20.0, 10.0 Hz, 3-H), 3.65 (3H, s, OMe), 3.30 (3H, s, OMe), 3.32-3.10 (4H, m, 3-H, 4-H and $PhCH_2$), 2.82 (1H, dd, J = 13.7, 9.0 Hz) and 2.71 (1H, dd, J = 11.0, 10.0 Hz), $PhCH_2$, 1.15 (9H, s, t-Bu)[Found: C, 66.7; H, 6.0; N, 2.3 $C_{33}H_{35}CrNO_6$ requires C, 66.8; H, 5.9; N, 2.4%].

Tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloyl-1,4-di(propyl)isoquinoline] chromium (0) (19, R=Pr)

^{n}Butyllithium (1.49 M in hexanes; 0.92 cm^3, 0.137 mmol) was added to a stirred solution of tricarbonyl-η^6-[1,2,3,4-tetrahydro-6,7-dimethoxy-2-pivaloyl-1-propylisoquinoline]chromium (0) (50 mg, 0.11 mmol) in tetrahydrofuran (1.0 ml), at -70°C, after 1h, 1-iodopropane (13.4 µl, 0.137 mmol) was added rapidly. A suspension formed and this was stirred for 5 min at -70°C, then warmed to room temperature. After 2h, the solvents were evaporated under reduced pressure and the residue purified by column chromatography on silica, eluting with 1:3 ethyl aceate/hexane, to give a yellow solid (9 mg, 16%), mp 188-190°C (dec.): υ_{max} (cm^{-1}) 1950, 1870, 1850, 1625; δ_H 5.40 (1H, dd, J = 10, 6.0 Hz, 1-H), 5.32 and 5.25 (2H, 2 x s, 5-H and 8-H), 4.26 (1H, br dd, J = 20.0, 12.7 Hz, 3-H), 3.81 (3H, s, OMe), 3.79 (3H, s, OMe), 3.10-2.90 (2H, m, 3-H and

4-H), 1.91-1.20 (8H, m, 2 x CH_2CH_2), 1.32 (9H, s, t-Bu), 1.03 (3H, t, J = 7.0 Hz, CH_3), 0.95 (3H, t, J = 7 Hz, CH_3)[Found : C, 60.0; H, 7.1; N, 2.7 $C_{25}H_{35}CrNO_6$ requires C, 60.3; H, 7.1; N, 2.8%].

1,2,3,4-Tetrahydro-6,7-dimethoxy-1-(3-methoxybenzyl)-2-pivaloylisoquinoline (17, R=OMe)
Potassium hexamethyldisilazide (0.5 M in toluene; 0.44cm^3) was added to a stirred suspension of tricarbonyl-η^6-[1,2,3,4-tetrahydro-1-(hydroxyphenylmethyl)-6,7-dimethoxy-2-pivaloylisoquinoline)] chromium (0) (52 mg) in THF (4 cm^3) at -78°C, under argon. After 1h, 3-methoxybenzyl chloride (0.15cm^3) was added, and after a further 1h at -78°C, the solution was warmed to -25°C and left for 18h. The solvents were removed and the residue was eluted through a column of silica eluting with 1:1 ethyl acetate/hexane. The eluant was exposed to air and sunlight for 18h, then passed down a short column of silica, eluting with ethyl acetate to afford a gum (17 mg, 43%): δ_H (400 MHz) 7.15 (1H, t, J = 7.0 Hz, 5′-H), 6.75 (2H, m, 4′-H and 6′-H), 6.69, 6.55 and 6.12 (3H, 3 x s, 5-H, 8-H and 2′-H), 5.70 (1H, br m, 1-H), 4.20 (1H, br m, 3-H), 3.82 (3H, s, OMe), 3.74 (3H, s, OMe), 3.56 (3H, s, OMe), 3.35 (1H, dt, J = 10.0, 3.0 Hz, 3-H), 3.10 (1H, dd, J = 10.0, 4.0 Hz, $PhCH_2$), 3.00 (1H, dd, J = 10.0, 6.3 Hz, $PhCH_2$), 2.90 (1H, ddd, J = 10.0, 7.0, 4.0 Hz, 4-H), 2.60 (1H, dt, J = 10.0, 3.0 Hz, 4-H), 1.24 (9H, s, t-Bu); δ_C 176.1 159.4, 147.6, 146.8, 139.75, 129.0, 128.5, 126.15, 122.4, 112.1, 111.0, 110.7, 77.1, 55.7, 55.5, 55.1, 42.1, 37.8, 30.4, 28.6 and 28.2; *m/z* (CI) M^++1 389 (35%), 276(35%).

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