Synthesis and chemical transformation of 2-iodomethyl-1-(phenylmethyl)-1,5,6,7-tetrahydroindol-4-ones

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2-Allyl-3-benzylamino-2-cyclohexenones undergo iodine-methanol–promoted iodocyclisation under reflux to afford products characterised by combination of NMR (^{1}H and ^{13}C), IR and mass spectroscopic techniques as the conjugated iodolium betaine derivatives of 2-iodomethyltetrahydroindolones. The zwitterionic nature of the products in solution and in the solid state was also confirmed by their chemical behaviour and the experimental data were corroborated by information from quantum chemical calculations.

Keywords: 2-allyl-3-benzylamino-2-enones, iodocyclisation, 2-iodomethyl-1-(phenylmethyl)-1,5,6,7-tetrahydroindol-4-ones

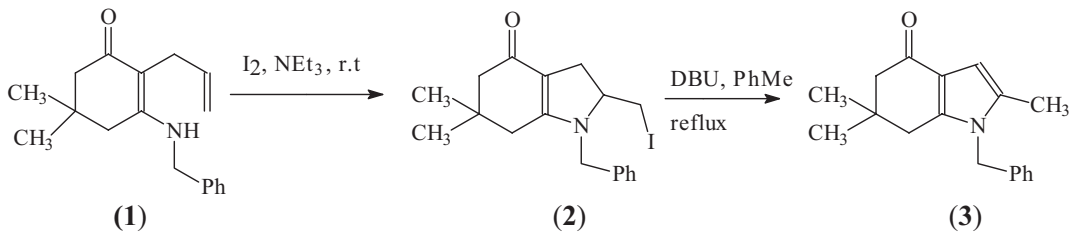
Several methods continue to appear in the literature describing the synthesis of substituted 4-oxo-4,5,6,7-tetrahydroindoles,[1-4] which are themselves suitable substrates for the construction of 4-substituted indole derivatives. Ferraz and coworkers,[5] have previously reported the results of the reaction of 2-allyl-β-benzylaminodimedone **1** with an I_2-NEt_3 mixture to afford 2-iodomethyl-6,6-dimethyl-1-(phenylmethyl)indol-4-one **2** followed by dehydrohalogenation with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) to form 4-oxo-6,7-dihydroindole **3** in 87% yield (Scheme 1). However, these authors did not provide the corresponding analytical data and the yield for compound **2**, which is implicated in the reaction. Furthermore, the generality of this reaction has not been demonstrated.

Previously in our laboratory, we employed iodine in refluxing methanol to effect iodoenolcyclisation and oxidative aromatisation of 2-allyl-1,3-cyclohexanedione derivatives to afford mixtures of the corresponding 2-iodomethyltetrahydrobenzofuran-4-one (minor) and 2-iodomethyldihydrobenzofuran derivatives (major).[6] The scant attention paid in the literature to the synthesis of compounds of the generalised structure **5** prompted us to extend the iodine-methanol reaction conditions to variously substituted 2-allyl-β-aminobenzyl-2-cyclohexenones **4** with the aim of preparing a series of 2-iodomethyl-1-(phenylmethyl)indol-4-ones or their indole derivatives for further studies of chemical transformations.

Results and discussion

To explore the scope of iodine-methanol–promoted electrophilic cyclisation, we subjected specially prepared 3-benzylamino-2-(pro-2-penyl)cyclohex-2-enone derivatives **4a**–**d** to iodine (1.2 equiv.) in methanol under reflux (Scheme 2). Work-up and solvent evaporation afforded crude products in high purity according to ^{1}H NMR and ^{13}C NMR spectroscopic data and these compounds deteriorated upon attempted recrystallisation. The significant aspects of the spectral data that are characteristic for these products, is the presence of a weak broad signal in the region δ_H 9.5–11.5 ppm of the ^{1}H NMR spectra obtained in $CDCl_3$ solution and the absence of bands corresponding to the carbonyl group in the IR spectra. The ^{13}C NMR spectra obtained in $CDCl_3$ solution are characterised by the presence of the aliphatic and aromatic signals and two resonances significantly downfield at δ_C *ca* 173.0 and 183.0 ppm corresponding to C-7a and C-4, respectively. The IR spectra of neat samples lack the carbonyl absorption bands and show the presence of an intense band in the region ν_{max} 1573–1578 cm^{-1}, which is characteristic of the C=C–C=N framework. The experimentally determined accurate *m/z* values represent in each case the closest fit consistent with the incorporation of a single iodine atom. The absence of the carbonyl band and the hydroxyl band in the IR spectra of these compounds ruled out the possibility of the 4-oxo structure **5** or its enol tautomer. Based on information from NMR (^{1}H and ^{13}C), IR and mass spectroscopy and in analogy with Soroka's physical vinologous amide–betaine–hydrogen-bonded betaine (VBHB) model,[7] we believe that products **5** exist in two of three possible structures, namely, that approximating to the vinologous amide **A**, that approximating to the betaine **B**, A and B being possible resonance structure and the solvated betaine **C** (Scheme 2). The absence of C=O and O–H absorption bands in the IR spectra of products **5** recorded as powders supports the approximation to the resonance hybrid **B** in the solid state. On the other hand, in $CDCl_3$ the situation seems to favour the solvated zwitterionic species **C** presumably due to coordination with the solvent molecules ($CHCl_3$) as confirmed by the weak broad signal in the region δ_H 9.5–11.5 ppm.

It was also interesting to observe that compounds **5a**, **b** and **d** undergo slow aromatisation on silica gel column accompanied by decomposition to afford low yields of the corresponding 4-hydroxy-2-iodomethyldihydroindole



(1) **(2)** **(3)**

Scheme 1

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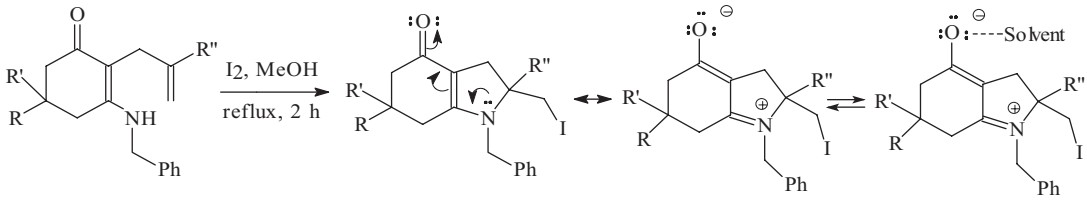


(**4**) (vinologous amide **A**) (betaine **B**) (solvated betaine **C**)

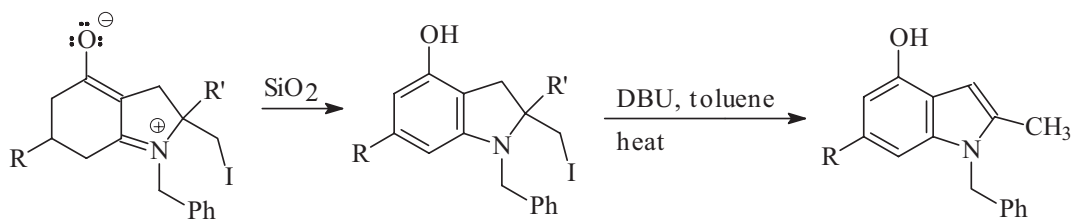
	R, R'	R"	% Yield (**5**)
a	H, H	H	99
b	H, CH_3	H	97
c	CH_3, CH_3	H	95
d	H, H	CH_3	98

Scheme 2

derivatives **6**. Our interest to explore the synthetic applications of these products in combination with a general demand for novel substances, which could potentially interact with biological systems prompted us to undertake further studies of their chemical transformations. Several attempts to dehydrohalogenate systems (**5**) under similar reaction conditions previously employed by Ferraz and coworkers have in our case led to complicated mixtures of products. However, when we subjected the dihydroindoles **6a** and **b** to DBU (2 equivalents) in toluene under reflux we isolated the corresponding 1-benzyl-4-hydroxy-2-methylindoles **7** as sole products and in appreciable yields (Scheme 3). Products **7** are easily distinguished from the corresponding precursors by the presence of the methyl and olefinic proton signals in their ^{1}H NMR spectra in the regions δ 2.40–2.50 ppm and δ 6.00–6.50 ppm, respectively

A possible explanation for the divergence in the reactions of systems **4** and the analogous 2-allyl-1,3-cyclohexanediones[6] is presumably the consequence of the increased propensity of nitrogen for electron pair delocalisation. This interaction which favours structure (**B**) would completely inhibit iodine-methanol–promoted oxidative aromatisation of the cyclohexenone moiety. The observed aromatisation of **5** to **6** during column chromatography further strengthen the exclusive nature of products **5** as the conjugated indolium betaines and their envisaged existence as **C** in a polar medium. In the absence of suitable crystalline material for X-ray analysis to confirm our argument, we opted for the application of density functional calculations. Using different starting geometry close to the structure of vinologous amide **A** and geometry close to structure of betaine **B** always yielded one and the same minimum, which was also confirmed by a vibration calculation. The resultant structure is a hybrid structure intermediate between vinologous **A** and betaine **B** which is closer to the latter. To lower the cost of calculations the iodine atom and the phenyl group, which are remote from the cyclohexenone moiety were replaced by hydrogen atoms. A single run was performed on the betaine before and after replacement of iodine and the phenyl group to confirm that this replacement will not affect the results. Full geometry optimisations were then performed for the betaine and betaine–$CHCl_3$ complex. The B3LYP/6-31 + + G(d,p) optimised structures for the stationary points for betaine and solvated betaine are included in Fig. 1 and the corresponding geometrical parameters are presented in the Table.

Modelling of solvated betaine (**B**) (one molecule of $CHCl_3$ with (**B**)) at the MP2/6-31 + G(d,p)//B3LYP/6-31 + + G(d,p) level which is corrected for BSSE also revealed the presence of a H-bond (see Fig. 1) of considerable strength (–6.188 kcal mol^{-1} and 2.001 Å). This corroborates the observed weak broad peak between δ 10 and 11.5 ppm corresponding to the hydroxyl proton of the envisaged solvated betaine **C** in the ^{1}H NMR spectra obtained in $CDCl_3$ solution. The vibrational frequencies of betaine were also computed at the B3LYP/6-31



(**5**) (**6**) (**7**)

	R	R'	% Yield (**6**)	% Yield (**7**)
(**a**)	H	H	40	77
(**b**)	CH_3	H	35	60
(**c**)	H	CH_3	30	–

Scheme 2

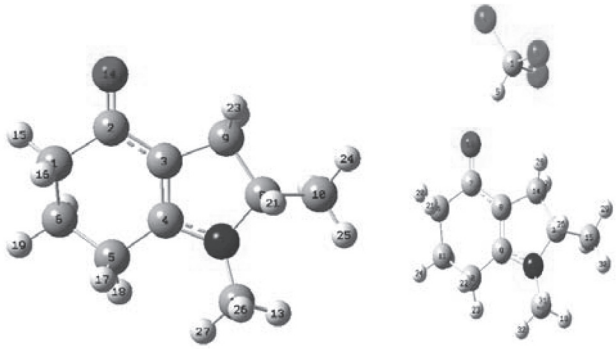


Fig. 1 Optimised structures of betaine and solvated betaine.

Table 1 Selected optimised geometrical parameters for model structures of betaine (B) and betaine–$CHCl_3$ complex C at the B3LYP/6-31 + + G(d,p) level[a]

Description	Betaine (**B**)	Betaine–$CHCl_3$ (**C**)
R(1,2)	1.533	1.530
R(1,6)	1.536	1.536
R(2,3)	1.443	1.434
R(2,14)	1.236	1.243
R(3,4)	1.369	1.373
R(4,7)	1.378	1.370
R(7,8)	1.490	1.490
R(8,9)	1.551	1.552
A(2,1,6)	113.1	113.1
A(2,1,15)	107.8	107.8
A(3,2,14)	123.3	123.6
A(2,3,4)	123.4	123.1
A(3,4,7)	112.2	112.1
A(4,5,6)	110.1	110.1
D(6,1,2,14)	152.6	153.1
D(14,2,3,4)	–179.7	179.8
D(14,2,3,9)	–1.5	–1.4
D(2,3,4,7)	179.8	–179.5
D(3,4,7,8)	11.6	10.4

[a]Atomic numbering is shown in Fig. 1, bond lengths are given in Angstrom and bond angles in degrees.

+ + G(d,p) level and a simulated IR spectrum (see Fig. 2a) plotted using GaussSum.[8,9] The simulated IR spectrum in the gas phase compares favourably with experimental spectrum for the solid compound recorded neat (Fig. 2b).

In summary, we have exploited the electrophilic properties associated with iodine to promote *exo*-trig cyclisation of the 3-benzylamino-2-(prop-2-enyl)cyclohexenones to afford the tetrahydroindolone derivatives in high yields according to Baldwin's rules.[10] Whereas the 2-allylcyclohexane-1,3-diones were found to undergo haloenolcyclisation and subsequent oxidative aromatisation under similar conditions,[6] the divergence of the 3-benzylamino-2-(propen-2-yl)cyclohexenones is attributed to strong C_{2P}–N_{2P} pi bond interaction. NMR and FT-IR spectroscopic data all point to the exclusive zwitterionic nature of the title compounds. Moreover, the results from quantum chemical calculations point to the preponderance of the conjugated indolium betaine structure in agreement with the experimental data.

Experimental

Solvents and commercially available reagents were purified by conventional methods before use. Melting points were determined on a Gallenkamp melting point apparatus and are uncorrected. For column chromatography, Merck kieselgel 60 (0.063–0.200 mm) was used as stationary phase. NMR spectra were obtained in $CDCl_3$ solutions using a Varian Mercury 300 MHz NMR spectrometer and the chemical shifts are quoted relative to the solvent peaks (δ_H 7.25 and δ_C 77.0 ppm). Low- and high-resolution mass spectra were recorded at an ionisation potential of 70eV using a Micromass

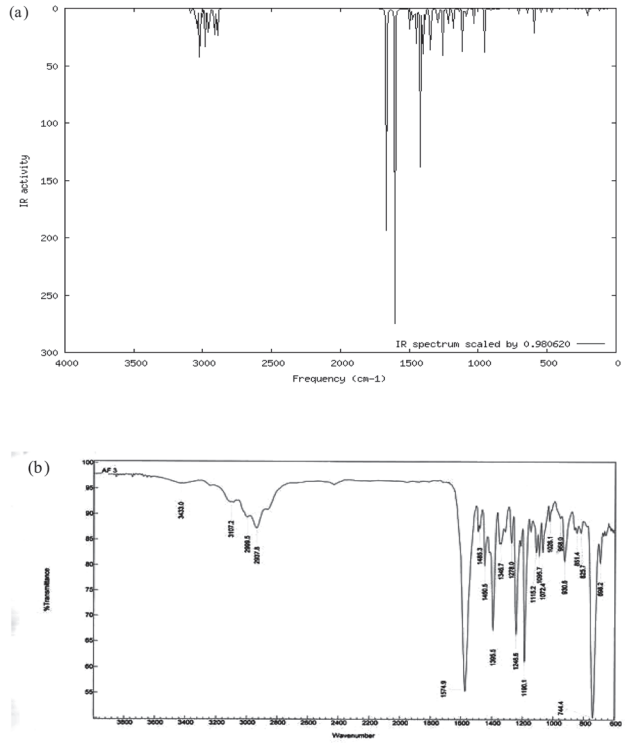


Fig. 2 (a) Simulated IR spectrum for betaine in the gas phase at the level B3LYP/6-31 + + G(d,p), (b) IR spectrum of **2a**.

Autospec-TOF (double focusing high resolution) instrument. The syntheses of substrates **4a**[4] and **4c**[5] have been described before and substrates **4b** and **4d**, which are new were prepared as follows.

General procedure for the synthesis of **4**

3-Benzylamino-5-methylcyclohex-2-enone (**4b**): A stirred mixture of 5-methyl-2-(prop-2-enyl)cyclohexane-1,3-dione (2.0 g, 12.3 mmol), *p*-TsOH (0.0014 g, 0.06 mmol) and benzylamine (1.93 g, 18.1 mmol) in benzene (250 ml) was boiled under Dean–Stark conditions for 18 h and then allowed to cool to room temperature. The solvent was evaporated under reduced pressure and the residue was taken up into chloroform and the organic solution was washed with water and then dried ($MgSO_4$). The salt was filtered off and the organic solvent was evaporated under reduced pressure and the residue was purified by column chromatography (EtOAc) to afford **1b** (2.14 g, 70%) as solid, m.p. 94–96°C; δ_H (300 MHz, $CDCl_3$) 1.02 (3H, d, J = 6.0 Hz), 1.96–2.15 (3H, m), 2.38–2.59 (2H, m), 3.09 (1H, dd, J = 6.3 and 16.2 Hz), 3.18 (1H, dd, J = 6.0 and 16.4 Hz), 4.42 (2H, dd, J = 1.8 and 6.2 Hz), 4.94–5.01 (2H, m), 5.19 (1H, br s), 5.65–5.78 (1H, m), 7.19–7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.3, 27.2, 28.6, 33.4, 44.4, 46.9, 106.3, 114.5, 126.6, 127.7, 128.9, 136.6, 138.1, 161.4, 194.0; ν_{max}/cm^{-1} 723, 1130, 1342, 1531, 1584, 1640, 3308; MS (EI) *m/z* 255 (M^+, 36.0), 240 (51.4), 91 (100), 28 (75.2). HRMS (EI) calculated for $C_{17}H_{21}ON$: 255.1623. Found: 255.1623.

3-Benzylamino-2-(2-methylprop-2-enyl) cyclohex-2-enone (**4d**): A mixture of 2-(2-methyl-2-propenyl)-1,3-cyclohexanedione (3 g, 18.1 mmol), benzylamine (1.94 g, 18.1 mmol) and *p*-TsOH (0.002 g, 0.09 mmol) in benzene (300 ml) was treated as described for **4b**. Column chromatography (EtOAc) afforded **4d**, solid (3.0 g, 65%), m.p. 82–84°C; δ_H (400 MHz, $CDCl_3$) 1.66 (3H, s), 1.91 (2H, quint., J = 6.3 Hz), 2.34 (2H, t, J = 6.6 Hz), 2.44 (2H, t, J = 6.3 Hz), 3.16 (2H, s), 4.41 (2H, d, J = 6.0 Hz), 4.68 (1H, d, J = 1.2 Hz), 4.73 (1H, d, J = 1.2 Hz), 5.32 (1H, br s), 7.18–7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 21.3, 21.5, 25.4, 31.3, 36.1, 46.9, 106.7, 110.2, 126.5, 127.1, 127.6, 128.5, 128.9, 138.1, 162.5, 194.3; ν_{max}/cm^{-1} 1178, 1376, 1526, 1642, 3283; MS (EI) *m/z* 255 (M^+, 81), 240 (97), 212 (62), 164 (44), 91 (100). HRMS (EI) calculated for $C_{17}H_{21}ON$: 255.1623. Found: 255.1613.

General procedure for iodocyclisation

A stirred mixture of **4** (1 equiv.) and iodine (1.5 equiv.) in methanol (5 ml per mmol of allylcyclohexenone) was boiled under reflux for

2 h. The mixture was allowed to cool and then poured into saturated aqueous sodium thiosulfate solution. Chloroform was added and the organic solution was washed with sodium bicarbonate and brine and then dried (Na_2SO_4). The salt was filtered off and the solvent was evaporated under reduced pressure to afford spectroscopically pure product **5**.

2-Iodomethyl-1-(phenylmethyl)-1,5,6,7-tetrahydroindol-4-one (**5a**): Reaction of **1a** with I_2–MeOH followed by aqueous work-up and solvent evaporation under reduced pressure afforded **5a**, solid (99%), m.p. 84–86°C; δ_H (300 MHz, $CDCl_3$) 2.05 (2H, quint., J = 6.3 Hz), 2.51–2.58 (2H, m), 2.66 (2H, t, J = 6.3 Hz), 3.01 (1H, dd, J = 6.6 and 15.0 Hz), 3.40 (1H, dd, J = 4.8 and 11.1 Hz), 3.54 (1H, dt, J = 4.5 and 11.3 Hz), 4.86 (2H, d, J = 6.3 Hz), 4.98–5.07 (1H, m), 7.27–7.36 (4H, m), 7.45 (1H, d, J = 6.6 Hz); δ_C (75 MHz, $CDCl_3$) 8.1, 20.6, 23.8, 26.3, 35.1, 47.6, 86.5, 109.4, 128.0, 128.3, 129.1, 134.4, 173.2, 184.0; ν_{max}/cm^{-1} 744, 1190, 1247, 1396, 1575, 2938; MS (EI) *m/z* 367 (M^+, 36), 365 (51), 254 (85), 241 (75), 226 (82.0), 212 (59), 150 (53), 127 (43), 91 (100), 65 (42). HRMS (EI) calculated for $C_{16}H_{18}NOI$: 367.0433. Found: 367.0430.

2-Iodomethyl-6-methyl-1-(phenylmethyl)-1,5,6,7-tetrahydroindol-4-one (**5b**): Reaction of **4b** with I_2–MeOH followed by aqueous work-up and solvent evaporation under reduced pressure afforded **5b** as mixture of diastereomers by ^{13}C NMR, solid (97%), m.p. 112–114°C; δ_H (300 MHz, $CDCl_3$) 1.07 (3H, d, J = 6.6 Hz), 1.78–2.72 (6H, m), 2.91–3.08 (1H, m), 3.27–3.38 (1H, m), 4.63 (2H, dd, J = 15.6 and 24.3 Hz), 4.74–4.87 (1H, m), 7.16–7.30 (5H, m); δ_C (75 MHz, $CDCl_3$) 8.2, 9.2, 21.0, 21.3, 29.5, 29.8, 31.3, 31.6, 32.4, 44.9, 54.1, 82.3, 83.7, 111.6, 112.6, 126.3, 127.4, 128.2, 140.8, 164.1, 164.6, 176.3; ν_{max}/cm^{-1} 748, 1223, 1578, 2930; MS (EI) *m/z* 381 (M^+, 10.0), 379 (14.0), 254 (87.4), 226 (74.5), 164 (68.0), 128 (65.0), 127 (71.5), 91 (100), 77 (25.5), 65 (51.8), 45 (48.5). HRMS (EI) calculated for $C_{17}H_{20}NOI$: 381.0590. Found: 381.0580.

2-Iodomethyl-6,6-dimethyl-1-(phenylmethyl)-1,5,6,7-tetrahydroindol-4-one (**5c**): Reaction of **4c** with I_2–MeOH followed by aqueous work-up and solvent evaporation under reduced pressure yielded (**5c**), oil (95%); δ_H (300 MHz, $CDCl_3$) 1.01 (3H, s), 1.05 (3H, s), 2.69 (1H, ddt, J = 2.4, 6.6 and 15.0 Hz), 3.10 (1H, ddt, J = 2.4, 9.9 and 15.0 Hz), 3.34 (2H, ddd, J = 2.1, 8.6 and 14.9 Hz), 4.73–4.83 (1H, m), 7.15–7.36 (5H, m); δ_C (75 MHz, $CDCl_3$) 8.9, 27.8, 28.4, 34.3, 34.8, 37.4, 39.8, 47.5, 86.3, 107.9, 126.5, 127.7, 128.2, 129.9, 134.9, 172.4, 182.7; ν_{max}/cm^{-1} 747, 1231, 1578, 2959; MS (EI) *m/z* 395 (M^+, 5.0), 269 (50.0), 254 (84.0), 240 (27.5), 91 (100). HRMS (EI) calculated for $C_{18}H_{22}NOI$: 395.0746. Found: 395.0742.

Iodomethyl-2-methyl-1-(1-phenylmethyl)-1,5,6,7-tetrahydroindol-4-one (**5d**):Reaction of **4d** with I_2–MeOH followed by aqueous work-up and solvent evaporation under reduced pressure yielded **5d**, solid (98%) m.p. 131–133°C; (300 MHz, $CDCl_3$) 1.71 (3H, s), 2.05 (2H, quint., J = 6.3 Hz), 2.53 (2H, q, J = 6.0 Hz), 2.64 (2H, s), 3.34 (2H, s), 3.47 (1H, q, J = 6.4 Hz), 4.87 (2H, d, J = 6.6 Hz), 7.25–7.48 (5H, m), 11.08 (1H, br s); δ_C (75 MHz, $CDCl_3$) 13.8, 20.6, 23.9, 26.2, 39.9, 47.5, 93.8, 108.9, 128.0, 128.3, 129.0, 134.5, 173.1, 182.8; ν_{max}/cm^{-1} 745, 1287, 1385, 1567, 2864, 2990, 3098; MS (EI) *m/z* 381 (M^+, 9), 379 (41), 255 (65), 254 (74), 240 (88), 238 (35), 212 (52), 164 (38), 127 (37), 65 (38). HRMS (EI) calculated for $C_{17}H_{20}NOI$: 381.0590. Found: 381.0580.

Silica gel–promoted aromatisation of (**5**): The crude iodocyclisation products were subjected to silica gel column using ethyl acetate as eluent. The following products were isolated:

4-Hydroxy-2-iodomethyl-1-(phenylmethyl)-2,3-dihydroindole (**6a**): Isolated as solid (40%), m.p. 73–75°C; δ_H (300 MHz, $CDCl_3$) 2.81 (1H, dd, J = 6.3 and 15.3 Hz), 3.18 (1H, dd, J = 9.0 and 15.2 Hz), 3.31 (1H, dd, J = 8.1 and 9.9 Hz), 3.45 (1H, dd, J = 4.8 and 9.9 Hz), 3.73 (1H, br s), 4.36 (3H, s), 4.88–4.99 (1H, m), 6.22 (1H, d, J = 8.4 Hz), 6.25 (1H, d, J = 8.4 Hz), 7.01 (1H, t, J = 8.1 Hz), 7.27–7.39 (5H, m); δ_C (75 MHz, $CDCl_3$) 9.20, 33.7, 48.2, 81.8, 99.7, 103.6, 127.4, 127.6, 128.6, 128.7, 129.5, 139.1, 145.0, 159.8; ν_{max}/cm^{-1} 756, 953, 1170, 1234, 1333, 1508, 1617, 3428. HRMS (EI) calculated for $C_{16}H_{16}NOI$: 365.0277. Found: 365.0276.

4-Hydroxy-2-iodomethyl-6-methyl-1-(phenylmethyl)-2,3-dihydroindole (**6b**): Isolated as solid (35%), m.p. 113–116°C; δ_H (300 MHz, $CDCl_3$) 2.24 (3H, s), 2.77 (1H, dd, J = 6.3 and 14.9 Hz), 2.14 (1H, dd, J = 9.6 and 14.7 Hz), 3.30 (1H, dd, J = 8.4 and 9.9 Hz), 3.43 (1H, dd, J = 4.8 and 9.9 Hz), 4.35 (3H, s), 4.88–4.94 (1H, m), 6.07 (1H, s), 6.09 (1H, s), 2.29–7.38 (5H, m); δ_C (75 MHz, $CDCl_3$) 9.3, 22.0, 33.5, 48.3, 82.0, 100.6, 104.4, 106.1, 127.4, 127.7, 128.7, 139.2, 140.0, 144.7, 160.0; ν_{max}/cm^{-1} 733, 801, 967, 1231, 1349, 1449, 1520, 3424. HRMS (EI) calculated for $C_{17}H_{18}NOI$: 379.0433. Found: 379.0433.

4-Hydroxy-2-iodomethyl-2-methyl-1-(phenylmethyl)-2,3-dihydroindole (**6d**): This compound was isolated as solid (30%), m.p. 112–114°C; δ_H (300 MHz, $CDCl_3$) 1.68 (3H, s), 2.84 (1H, d, J = 15.3 Hz), 3.11 (1H, d, J = 15.0 Hz), 3.44 (2H, s), 4.36 (2H, s), 6.22 (1H, J = 6.0 Hz), 6.24 (1H, d, J = 6.3 Hz), 7.02 (1H, t, J = 8.1 Hz), 7.29–7.40 (5H, m); δ_C (75 MHz, $CDCl_3$) 15.7, 26.3, 38.8, 48.2, 86.7, 100.0, 103.3, 127.4, 127.6, 128.7, 129.5, 139.1, 145.1, 159.1; ν_{max}/cm^{-1} 751, 1240, 1346, 1462, 1601, 1620, 3424; HRMS (EI) calculated for $C_{17}H_{18}NOI$: 379.0433. Found: 379.0437.

General procedure for the dehydrohalogenation of **6a** *and* **6b**

A stirred solution of the iodomethyl derivative **6** (1 equiv.) in toluene (5 ml per mmol of iodo derivative) was treated with DBU (2 equiv.). The mixture was refluxed for 18 h with the exclusion of moisture and then allowed to cool. The cold mixture was quenched with water and then extracted with chloroform (3 × 20 ml). The combined organic extracts were washed with saturated ammonium chloride solution, dried (Na_2SO_4), filtered and then evaporated under reduced pressure. The residue was purified by column chromatography on silica gel (EtOAc) to afford the corresponding dehydrohalogenated product.

4-Hydroxy-2-methyl-1-(phenylmethyl)-1H-indole (**7a**): Reaction of **6a** with DBU followed by column chromatography (EtOAc) yielded **5a** solid (77%), m.p. 72–74°C; δ_H (300 MHz, $CDCl_3$) 2.43 (3H, s), 4.09 (1H, br s), 4.45 (2H, s), 6.29 (1H, d, J = 1.0 Hz), 6.39 (1H, d, J = 8.1 Hz), 6.86 (1H, dd, J = 0.6 and 8.3 Hz), 7.06 (1H, t, J = 7.8 Hz), 7.25–7.43 (5H, m); δ_C (75 MHz, $CDCl_3$) 14.0, 48.5, 99.0, 101.1, 103.1, 116.7, 124.3, 127.3, 127.6, 128.6, 139.3, 141.0, 153.2, 155.5; ν_{max}/cm^{-1} 767, 1248, 1357, 1500, 1597, 3412; MS (EI) *m/z* 237 (M^+, 100), 146 (98), 91 (77.0). 28 (60.0). HRMS (EI) calculated for $C_{16}H_{15}NO$: 237.1154. Found: 237.1153.

4-Hydroxy-2,6-dimethyl-1-(phenylmethyl)-1H-indole (**7b**): Reaction of **6b** with DBU followed by column chromatography (EtOAc) yielded **7b** as an oil (60%); δ_H (300 MHz, $CDCl_3$) 2.36 (3H, s), 2.39 (3H, d, J = 1.2 Hz), 4.05 (1H, br s), 4.42 (2H, s), 6.22 (1H, t, J = 1.2 Hz), 6.24 (1H, s), 6.68 (1H, d, J = 0.9 Hz), 7.10–7.43 (5H, m); δ_C (75 MHz, $CDCl_3$) 14.0, 22.1, 48.5, 98.8, 101.6, 104.5, 114.3, 127.3, 127.7, 128.7, 134.6, 139.4, 140.6, 152.6, 155.9; ν_{max}/cm^{-1} 734, 801, 1119, 1216, 1592, 3412; MS (EI) *m/z* 251 (M^+, 100), 160 (97.0), 91 (63.0). HRMS (EI) calculated for $C_{16}H_{17}NO$: 251.1310. Found: 251.1311.

Computational methods

All calculations have been done using the GAUSSIAN 98W program package.[11] The 6-31 + + G(d,p) basis set, was used for geometry optimisation. The nature of all of the optimised stationary points was characterised by frequency calculations at the same level, which indicate that all structures are minima (no imaginary eigenvalues of the Hessian matrix) on the potential energy surface. The frequencies are consistently overestimated at B3LYP/6-31 + + (d,p), which is due to the neglect of correlation energy and presence of anharmonicity in the molecular vibrations. Therefore, frequencies were scaled by a factor 0.98062.[12] Hydrogen bonding strength of the betaine–$CHCl_3$ complex has been computed at the level of MP2/6-31 + G(d,p)// B3LYP/6-31 + + G(d,p). The hydrogen bonding energy was corrected for the BSSE.[13]

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References

1 P. Barraja, P. Diana, A. Lauria, A. Montalbano, A.M. Almerico, G. Dattolo, G. Cirrincione, G. Viola and F. Dall'Acqua, *Bioorg. Med. Chem. Lett.*, 2003, **13**, 2809.
2 D.R. Hutchinson, N.K. Nayyar and M.J. Martinelli, *Tetrahedron Lett.*, 1996, **37**, 2887.
3 N.K. Nayyar, D.R. Hutchinson and M.J. Martinelli, *J. Org. Chem.*, 1997, **62**, 982.
4 H. Iida, Y. Yuasa and C. Kibayashi, *Tetrahedron Lett.*, 1982, **23**, 3591.
5 H.M.C. Ferraz, F.L.C. Pereira, F.S. Leite, M.R.S. Nunes and F.S. Payret-Arrua, *Tetrahedron,* 1995, **55**, 10915.
6 M.J. Mphahlele and T.B. Moekwa, *Org. Biomol. Chem.*, 2005, **3**, 2469.
7 E.K. Wróblewska, J.A. Soroka, K.B. Soroka and M. Gąsiorowska, *J. Phys. Org. Chem.*, 2005, **18**, 347.
8 N.M. O'Boyle, GaussSum 2.1, 2007. Available at http://gausssum.sf.net

9 N.M. O'Boyle, A.L. Tenderholt and K.M. Langner. *J. Comp. Chem*., 2008, **29**, 839.
10 J.E. Baldwin, *J. Chem. Soc., Chem. Commun.*, 1976, 734.
11 M.J. Frisch, G.W. Trucks, H.B. Schlegel, G.E. Scuseria, M.A. Robb, J.R. Cheeseman, V.G. Zakrzewski, J.A. Montgomery, Jr., R.E. Stratmann, J.C. Burant, S. Dapprich, J.M. Millam, A.D. Daniels, K.N. Kudin, M.C. Strain, O. Farkas, J. Tomasi, V. Barone, M. Cossi, R. Cammi, B. Mennucci, C. Pomelli, C. Adamo, S. Clifford, J. Ochterski, G.A. Petersson, P.Y. Ayala, Q. Cui, K. Morokuma, D.K. Malick, A.D. Rabuck, K. Raghavachari, J.B. Foresman, J. Cioslowski, J.V. Ortiz, A.G. Baboul, B.B. Stefanov, G. Liu, A. Liashenko, P. Piskorz, I. Komaromi, R. Gomperts, R.L. Martin, D.J. Fox, T. Keith, M.A. Al-Laham, C.Y. Peng, A. Nanayakkara, C. Gonzalez, M. Challacombe, P.M.W. Gill, B.G. Johnson, W. Chen, M.W. Wong, J.L. Andres, M. Head-Gordon, E.S. Replogle and J.A. Pople, Gaussian, Inc., Pittsburgh PA, 1998.
12 A.P. Scott and L.J. Radom, *J. Phys. Chem*., 1996, **100**, 16502.
13 S.F. Boys and F. Bernardi, *Mol. Phys*., 1970, **19**, 533.