Possible Neighbouring Group Participation of a Nitro-group in the Conversion of 3-Hydroxymethyl-2-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline into its 3-Chloromethyl derivative.

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The alcohol **12** reacted with 4-toluenesulfonyl chloride in boiling dichloromethane solution to give the chlorinated product **13** rather than the expected tosylate **3** by a mechanism that could involve neighbouring group participation of the nitro-substituent. In contrast, the isomeric alcohol **15** reacted normally with 4-toluenesulfonyl chloride giving the tosylate **16** under similar conditions.

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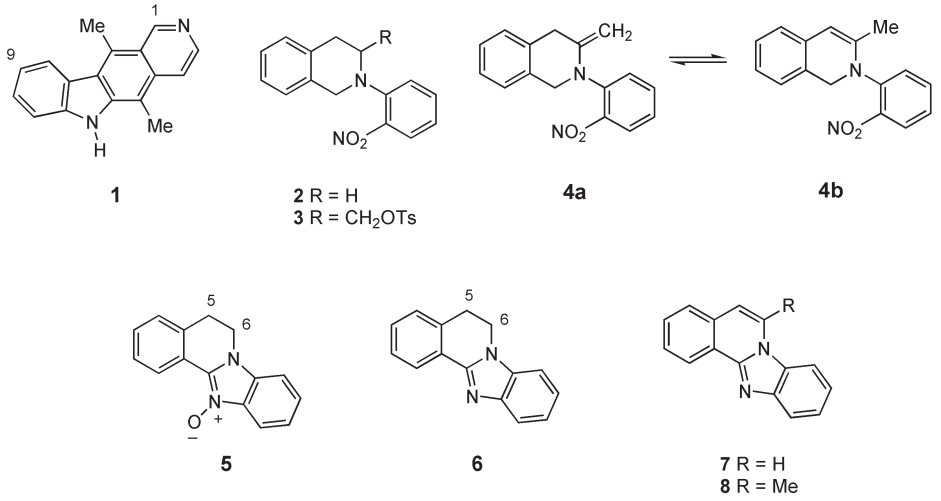
We have recently reported the preparation of a series of 5,6-dihydrobenzimidazo[2,1-*a*]isoquinoline derivatives **6** [1] and their corresponding *N*-oxide derivatives **5** [1,2] as part of a study of analogues of the anti-cancer agent Ellipticine (**1**) and its 9-oxygenated derivatives (Scheme 1) [1]. *N*-Oxides **5** were readily prepared by cyclodehydration of 2-(2-nitroaryl)-1,2,3,4-tetrahydroisoquinolines **2** in boiling propionic acid (the *t*-amino effect) [3] and deoxygenation of these compounds with phosphorus trichloride yielded derivatives of heterocyle **6** [1]. We were also interested in the preparation of the fully conjugated benzimidazo[2,1-*a*]isoquinolines **7** but the attempted oxidation of derivatives of heterocycles **6** were unsuccessful. Literature precedence suggested that this transformation might not be readily achieved because 2,3,9,10-tetramethoxybenzimidazo[2,1-*a*]isoquinoline had only been obtained in 10 % yield by palladium on carbon mediated dehydrogenation of the corresponding 5,6-dihydroderivative [4]. An alternative approach to these fully conjugated heterocycles was therefore sought.

The strategy we envisaged was to prepare the 4-toluenesulfonate derivative **3** from which the enamine **4a** might be obtained by base-induced elimination. Tautomerisation of this enamine might be then expected to yield the 6-methyl derivative **8** of compound **7** (Scheme 1). This note describes an unexpected reaction of the 4-toluenesulfonate derivative **3**.

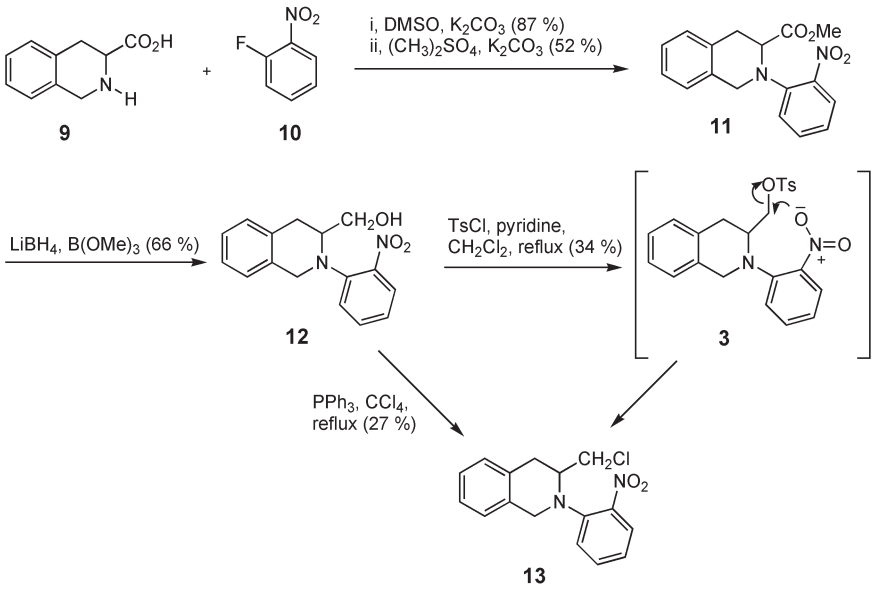
The synthetic route to the 4-toluenesulfonate derivative **3** is shown in Scheme 2. 1,2,3,4-Tetrahydroisoquinoline-3-carboxylic acid (**9**) was reacted with 2-fluoronitrobenzene (**10**) and the resulting carboxylic acid was esterified directly by treatment with dimethyl sulfate under basic conditions giving the ester **11**. Reduction of ester **11** was achieved by treatment with lithium borohydride in the presence of trimethoxyborane yielding the alcohol **12** [5]. When the alcohol **12** was treated with 4-toluenesulfonyl chloride in pyridine, unexpectedly, the chloride **13** was obtained. The formation of the chloride **13** has been rationalised as shown in Scheme 2 in which neighbouring group participation by the nitro-group results in a favourable 7-*endo-tet* intramolecular reaction [6] giving a putative cyclic intermediate that is then attacked by chloride yielding the product **13**. Compound **13** could also be prepared by an alternative route by the reaction of alcohol

Scheme 1



12 with carbon tetrachloride and triphenylphosphine thus confirming the structure of the chloride **13**.

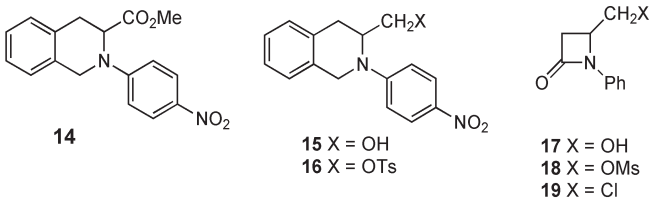
Scheme 2



In support of this mechanism involving neighbouring group participation by the nitro-group, the isomeric alcohol **15** was also prepared. In an analogous method to the preparation of ester **11**, treatment of compound **9** with 4-fluoronitrobenzene and subsequent esterification of the resulting acid gave the ester **14** which was then reduced with lithium borohydride affording the alcohol **15**. Reaction of this alcohol **15** with 4-toluenesulfonyl chloride, under identical conditions as those used for the transformation of compound **12** into compound **13**, gave the 4-toluenesulfonyl derivative **16** as expected.

Simig and co-workers have described the formation of the chloride **19** directly from the alcohol **17** in 53 % yield [7]. Their reaction conditions were harsh compared with ours and involved treating the alcohol **17** with methanesulfonyl chloride in boiling pyridine solution. Under milder conditions (pyridine and methanesulfonyl chloride with ice-cooling) these workers isolated the mesylate **18**.

Scheme 3



EXPERIMENTAL

Infra-red spectra were recorded as potassium bromide discs using a Perkin Elmer Paragon 1000 spectrophotometer. Proton NMR spectra were determined at 270 MHz in deuteriochloroform solution using a Jeol GX270 instrument. Elemental analyses were performed by the Department of Chemistry, University of Newcastle upon Tyne, UK. High resolution mass spectra were either performed at the EPSRC national mass spectrometry service centre, Swansea, UK (electrospray) or at the University of Newcastle upon Tyne, UK (electron impact).

Methyl 2-(2-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**11**).

To a stirred mixture of racemic 1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (**9**) (4.0 g, 22.7 mmol) and potassium carbonate (5.6 g, 40.7 mmol) in dimethylsulfoxide (20 mL) at room temperature was added 2-fluoronitrobenzene (**10**) (3.36 g, 23.8 mmol) in portions. The mixture was then heated at 100 °C (4 hours) with stirring, allowed to cool to room temperature and poured into water. The mixture was acidified with dilute hydrochloric acid to pH 1 at room temperature and then extracted with dichloromethane (3 x 50 mL). The organic fractions were washed several times with water, dried (magnesium sulfate) and evaporated giving the crude 2-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid (5.89 g, 87 %) as an orange solid, mp 141-143 °C (from ethanol). This compound had ir: 1699, 1602, 1508, 1334 and 1235 cm^{-1}; ^1H nmr: δ 7.82 (dd, 1H, J = 6 and 1 Hz, Ar-H), 7.55-7.00 (m, 7H, ArH), 4.80 (d, 1H, J = 9 Hz, 1-H), 4.35 (dd, 1H, J = 4 and 1 Hz, 3-H), 4.10 (d, 1H, J = 9 Hz, 1-H), 3.49 (dd, 1H, J = 9 and 4 Hz, 4-H) and 3.35 (dd, 1H, J = 9 and 1

Hz, 4-H). A mixture of this carboxylic acid (5.89 g, 19.8 mmol), potassium carbonate (4.0 g, 28.9 mmol) and dimethylsulfate (2.0 mL, 21.2 mmol) in acetone (20 mL) was heated at reflux (2 hours), allowed to cool to room temperature and then poured into water. The mixture was extracted with dichloromethane (3 x 50 mL), the organic extracts were washed with water, dried (magnesium sulfate) and evaporated giving the ester **11** (3.08 g, 52 %) as a yellow solid, mp 111-112 °C. Compound **11** had: ir: 1727, 1606, 1524, 1342, 1203 and 1164 cm^{-1}, ^1H nmr: δ 7.84 (d, 1H, J = 8 Hz, Ar-H), 7.57-7.44 (m, 2H, Ar-H), 7.19-7.06 (m, 5H, Ar-H), 4.92 (d, 1H, J = 15 Hz, 1-H), 4.31 (dd, 1H, J = 4 and 1 Hz, 3-H), 4.16 (d, 1H, J = 15 Hz, 1-H), 3.57 (s, 3H, $-CH_3$), 3.58 (dd, 1H, J = 16 and 4 Hz, 4-H) and 3.25 (dd, 1H, J = 16 and 1 Hz, 4-H); ms: m/z (electrospray positive) calcd. for $C_{17}H_{17}N_2O_4$ (M+H): 313.1184. Found: 313.1189.

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.1; N, 9.0. Found: C, 65.4; H, 4.6; N, 8.9.

3-Hydroxymethyl-2-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**12**) and 3-Chloromethyl-2-(2-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**13**).

To a stirred mixture of ester **11** (0.50 g, 1.6 mmol) and trimethoxyborane (0.02 mL, 0.16 mmol) in anhydrous ether (20 mL) at room temperature was added lithium borohydride (0.04 g, 1.8 mmol). The mixture was heated at reflux (4 hours) under an atmosphere of nitrogen, allowed to cool to room temperature and poured carefully into water and extracted with ether. The organic layer was washed with water, dried (magnesium sulfate) and evaporated giving compound **12** (0.30 g, 66 %) as an orange oil. Compound **12** had ir: 3500-3200 (broad), 1603, 1512, 1345, and 1045 cm^{-1}; ^1H-nmr: δ 7.82 (d, 1H, J = 7 Hz, Ar-H), 7.40 (t, 1H, J = 7 Hz, Ar-H), 7.22-6.95 (m, 6H, Ar-H), 4.58 (d, 1H, J = 16 Hz, 1-H), 4.12 (1H, m), 3.85-3.55 (m, 3H), 3.28 (dd, 1H, J = 12 and 6 Hz) and 2.78 (dd, 1H, J = 16 and 2 Hz). To a cooled (0 °C), stirred, mixture of compound **12** (0.50 g, 1.8 mmol) and triethylamine (0.62 mL, 4.4 mmol) in dichloromethane (25 mL) was added 4-toluenesulfonyl chloride (0.42 g, 2.2 mmol). The mixture was then heated at reflux (2 hours), allowed to cool to room temperature and poured into an excess of dilute hydrochloric acid. The organic layer was separated and the aqueous layer was extracted with dichloromethane (20 mL). The combined organic fractions were washed with water, dried (magnesium sulfate) and evaporated giving a brown oil (0.67 g). The oil was purified by column chromatography over silica gel (eluent: petroleum ether bp 60-80 °C: ethyl acetate, 20:1) giving the chloride **13** (0.18 g, 34 %) as a yellow solid, mp 100-103 °C. Compound **13** had ir: 1604, 1518, 1342, 1236, 1162 and 751 cm^{-1}; ^1H-nmr: δ 7.81 (d, 1H, J = 9 Hz, Ar-H), 7.47 (t, 1H, J = 8 Hz, Ar-H), 7.25-7.00 (m, 6H, Ar-H), 4.58 (d, 1H, J = 16 Hz, 1-H), 4.10 (d, 1H, J = 16 Hz, 1-H), 3.92, (m, 1H, 3-H), 3.67 (m, 1H, $-CH_2Cl$), 3.46 (dd, 1H, J = 6 and 2 Hz, $-CH_2Cl$), 3.44 (dd, 1H, J = 16 and 5 Hz, 4-H) and 2.90 (dd, 1H, J = 16 and 2 Hz, 4-H); ms: m/z (electron impact) calcd. for $C_{16}H_{15}N_2O_2Cl$: 302.0822. Found: 302.0826 (M^+).

Anal. Calcd. for $C_{16}H_{15}N_2O_2Cl$: C, 63.5; H, 5.0; N, 9.3. Found: C, 63.6; H, 4.7; N, 9.1.

Compound **13** was also prepared as follows. A mixture of alcohol **12** (0.25g, 0.9 mmol, triphenylphosphine (0.30 g, 0.9 mmol) and carbon tetrachloride (0.27 g, 1.7 mmol) in anhydrous dichloromethane (10 mL) was heated under reflux (4 hours) with stirring. The mixture was allowed to cool to room temperature and poured into water. The organic layer was separated and the aqueous layer was extracted with dichloromethane (10 mL). The combined organic fractions were washed with water, dried (magnesium sulfate) and evaporated giving an orange oil (0.21 g) which was purified by column chromatography over silica gel (eluent: petroleum ether bp 60-80 °C: ethyl acetate, 20:1) yielding compound **13** (0.07 g, 27 %), identical with an authentic sample.

Methyl 2-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylate (**14**).

Compound **14** was prepared using a similar procedure to that described above for the preparation of compound **11**. 2-(4-Nitrophenyl)-1,2,3,4-tetrahydroisoquinoline-3-carboxylic acid was prepared as an orange solid, mp 193-195 °C (ethanol) in 53 % yield and had: ir: 1715, 1597, 1484, 1317 and 1112 cm^{-1}; ^1H-nmr: δ 8.20 (d, 2H, J = 6 Hz, Ar-H), 7.30-7.15 (m, 4H, Ar-H), 6.82 (d, 2H, J = 6 Hz, Ar-H), 4.90 (dd, 1H, J 4 and 1 Hz, 3-H), 4.70 (d, 1H, J = 12 Hz, 1-H), 4.58 (d, 1H, J = 12 Hz, 1-H), 3.42 (dd, 1H, J = 10 and 1 Hz, 4-H), 3.35 (dd, 1H, J = 10 and 3 Hz, 4-H). Esterification of this acid gave compound **14** as a yellow solid, mp 149 °C (methanol) in 87 % yield. Compound **14** had: ir: 1743, 1601, 1488, 1347, 1200 and 1179 cm^{-1}; ^1H-nmr: δ 8.18 (d, 2H, J = 7 Hz, Ar-H), 7.30-7.15 (m, 4H, Ar-H), 6.80 (d, 2H, J = 7 Hz, Ar-H), 4.91 (dd, 1H, J = 4 and 1 Hz, 3-H), 4.73 (d, 1H, J = 12 Hz, 1-H), 4.60 (d, 1H, J = 12 Hz, 1-H), 3.59 (s, 3H, $-CH_3$), 3.40 (dd, 1H, J = 12 and 1 Hz, 4-H) and 3.32 (dd, 1H, J = 10 and 3 Hz, 4-H).

Anal. Calcd. for $C_{17}H_{16}N_2O_4$: C, 65.4; H, 5.1; N, 9.0. Found: C, 65.5; H, 5.0; N, 8.9.

3-Hydroxymethyl-2-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**15**) and 3-(4-Methylbenzenesulfonyloxymethyl)-2-(4-nitrophenyl)-1,2,3,4-tetrahydroisoquinoline (**16**).

Using a similar method to that described above, reduction of ester **14** gave compound **15** (74 %) as a yellow oil. Compound **15** had ir: 3500-3200 (broad), 1596, 1486, 1314 and 1112 cm^{-1}; ^1H-nmr: δ 8.18 (d, 2H, J = 9 Hz, Ar-H), 7.29-7.20 (m, 4H, Ar-H), 6.92 (d, 2H, J = 9 Hz, Ar-H), 4.58 (d, 1H, J = 16 Hz, 1-H), 4.43 (d, 1H, J = 16 Hz, 1-H), 4.42 (m, 1H), 3.60 (m, 1H), 3.40 (m, 1H) and 3.12 (m, 2H). Compound **15** was reacted with 4-toluenesulfonyl chloride in an analogous manner to compound **12** giving the tosylate **16** (42 %) as an orange solid, mp 160-162 °C after column chromatography over silica gel (eluent: petroleum ether bp 60-80 °C: ethyl acetate, 20:1). Compound **16** had ir: 1596, 1502, 1324, 1173, 1096 and 975 cm^{-1}; ^1H-nmr: δ 8.13 (d, 2H, J = 9 Hz, Ar-H), 7.65 (d, 2H, J = 9 Hz, Ar-H), 7.30-7.12 (m, 6H, Ar-H), 6.79 (d, 2H, J = 9 Hz, Ar-H), 4.53 (m, 1H), 4.48 (d, 1H, J = 16 Hz, 1-H), 4.29 (d, 1H, J = 16 Hz, 1-H), 3.90 (m, 1H), 3.61 (m, 1H), 3.11 (m, 2H) and 2.42 (s, 3H, $-CH_3$).

Anal. Calcd. for $C_{23}H_{22}N_2O_5S$: C, 63.0; H, 5.0; N, 6.4. Found: C, 63.1; H, 5.2; N, 6.4.

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