The Preparation and Oxidative Dimerisation of 2-Acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline. A New Approach to Tetrahydroisoquinoline Synthesis

J. F. Ajao and C. W. Bird*

Department of Chemistry, Queen Elizabeth College,
Campden Hill, London W8 7AH, U. K.

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The title compound has been prepared from 1,2,3,4-tetrahydroisoquinoline *via* successive nitration, acetylation, reduction and diazotisation. Earlier conflicting reports on the nitration of tetrahydroisoquinoline have been clarified. A better synthetic route, based upon reduction of the corresponding isocarbostyril, has been devised and should be applicable to the obtention of a wide range of tetrahydroisoquinolines. The structure of the neutral product of oxidative dimerisation of 2-acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline has been established.

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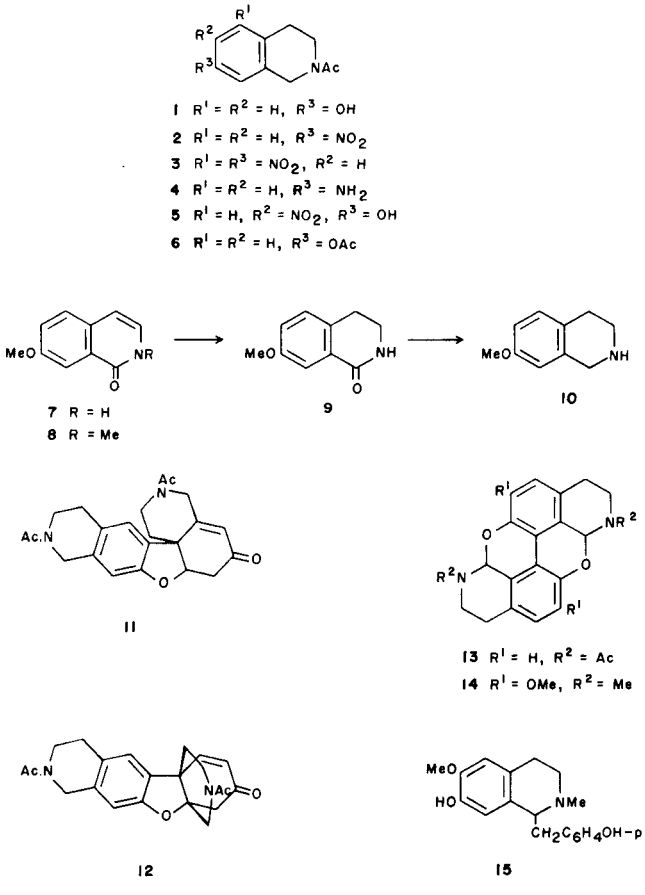
In connection with studies on the oxidative co-dimerisation of phenols [1] we undertook the synthesis of 2-acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline **1** and investigated its oxidative dimerisation.

Our initial approach to **1** was based upon the nitration of commercially available tetrahydroisoquinoline. Although nitration in sulfuric acid by addition of potassium nitrate was originally reported [2] to yield the 7-nitro derivative **2**, this was contradicted subsequently and the method claimed [3] to give only a small amount of a dinitro derivative. Instead the 7-nitro compound was reported to result from nitration with a mixture of nitric and sulfuric acids. However repetition of the nitration under these conditions, followed by acetylation of the crude products and subsequent chromatographic separation gave only a minor amount of **2** accompanied by a much larger quantity of 2-acetyl-5,7-dinitrotetrahydroisoquinoline **3**. The orientation of **3** was established by its formation from **2** on further nitration, and the observation of the aromatic protons as singlets at 8.38 and 8.72 ppm in the nmr spectrum. In contrast treatment of tetrahydroisoquinoline in sulfuric acid with a molar equivalent of potassium nitrate provided the required 7-nitro derivative **2**.

Catalytic hydrogenation of **2** gave the corresponding 7-amino compound **4**, but its subsequent conversion to the phenol **1**, through generation and decomposition of the diazonium salt gave only poor yields despite extensive efforts at improvement. Failure to destroy unreacted nitrous acid prior to decomposition of the diazonium salt led to formation of the nitrophenol **5**, whose structure is established by observation of singlets at δ 7.11 and 7.26 ppm for the aromatic protons in the ^{1}H nmr spectrum.

Consequently an alternative route to **1** was devised based upon reduction of 7-methoxyisocarbostyril **6**. Such an approach to the synthesis of tetrahydroisoquinolines does not appear to have been used previously despite the ready accessibility of isocarbostyrils from cinnamic acids *via* cyclisation of the derived styryl isocyanates [4,5]. The *p*-methoxystyryl isocyanate was generated by reaction of *p*-methoxycinnamyl chloride with sodium azide suspended in *m*-xylene. The subsequent cyclisation to **7** proceeded in refluxing *o*-dichlorobenzene containing a trace of iodine [5], with none of the trimer formation encountered under other conditions. Catalytic hydrogenation of **7** provided the dihydroisocarbostyril **8**, which on subsequent reduction with lithium aluminium hydride yielded 7-methoxytetrahydroisoquinoline **10**. Cleavage of the methoxyl



group with hydrobromic acid and acetylation formed 7-acetoxy-2-acetyltetrahydroisoquinoline **6**, which was finally *O*-deacetylated with activated zinc in methanol to give **1**. This alternative synthesis of **1** also provides experimental confirmation of the presumed position of nitration of the tetrahydroisoquinolinium cation.

Analogy with the course of oxidative self-coupling of 5,6,7,8-tetrahydro-2-naphthol [1] led us to anticipate that oxidation of **1** with potassium ferricyanide would yield the neutral dimers **11** and **12**. However, only a very small quantity of a single non-phenolic dimer resulted. The structure **13** may be assigned to this dimer on the basis of its ^{1}H nmr spectrum which, in addition to a 6-proton singlet at 2.21 ppm for the *N*-acetyl groups, consists of an 8-proton multiplet for the methylene groups at 2.86-3.19 ppm, a singlet at 5.29 ppm for the methine protons, and doublets at 6.95 and 7.37 (J = 8.7 Hz) ppm for the aromatic protons. An analogous product **14** has been obtained [7] from the oxidation of the tetrahydroisoquinoline derivative **15**.

EXPERIMENTAL

Nuclear Magnetic Resonance (^{1}H nmr) spectra were recorded at 60 MHz on a Perkin Elmer R12B or a Brucker WP60FT spectrometer. Infrared (ir) spectra were recorded for nujol mulls on a Pye-Unicam SP200 or a Perkin-Elmer 157 spectrophotometer. Mass spectra (ms) were determined by the ULIRS Mass Spectrometry Service at Queen Elizabeth College using an MS30 instrument. Melting points are uncorrected and were measured on a Gallenkamp melting point apparatus.

Nitration of Tetrahydroisoquinoline. (a) Using Concentrated Nitric and Sulfuric Acids.

Tetrahydroisoquinoline (12.2 g, 91.6 mmoles) was dissolved in concentrated sulfuric acid (40 ml) with cooling. Concentrated nitric acid (9 ml, d 1.35) was added dropwise to the stirred solution while maintaining the temperature below 5°. The reaction mixture was allowed to stand overnight at room temperature and then poured onto ice. The resulting solution was basified with aqueous ammonia and extracted with chloroform. The chloroform extracts were dried over sodium sulfate and evaporated *in vacuo*. The dark brown residue was dissolved in ethanol (90 ml) and concentrated hydrochloric acid (10 ml) added. The precipitated hydrochloride salts (14.1 g), anhydrous sodium acetate (5 g) and acetic anhydride (50 ml) were heated together on a steam bath for 3 hours and the reaction mixture then poured into water. The resulting acetyl derivatives were isolated by chloroform extraction, and chromatographed over silica gel using dichloromethane-methanol (20:1) as eluant. The first material eluted was 2-acetyl-7-nitro-1,2,3,4-tetrahydroisoquinoline (**2**) (10%) mp 84-86° from ethyl acetate (lit [2] 84-86°); ir: 1650, 1520, 1350 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.23 (s, 3H, $NCOCH_3$), 2.85-3.17 (m, 2H, H-4), 3.65-3.95 (m, 2H, H-3), 4.85 (s, 2H, H-1), 7.30-7.55 (m, 1H, ArH), 7.95-8.20 (m, 2H, ArH) ppm.

Anal. Calcd. for $C_{11}H_{12}N_2O_2$: C, 60.0; H, 5.45; N, 12.73. Found: C, 60.15; H, 5.48; N, 12.63.

The second compound eluted was 2-acetyl-5,7-dinitro-1,2,3,4-tetrahydroisoquinoline (**3**) (30%) mp 136-138° from ethyl acetate; ir: 1650, 1540, 1350 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.21 (s, 3H, $NCOCH_3$), 3.09-3.48 (m, 2H, H-4), 3.6-4.0 (m, 2H, H-3), 4.92 (s, 2H, H-1), 8.38 (s, 1H, ArH), 8.72 (s, 1H, ArH) ppm.

Anal. Calcd. for $C_{11}H_{11}N_3O_5$: C, 49.81; H, 4.18; N, 15.84. Found: C, 50.09; H, 4.18; N, 15.63.

(b) Using Potassium Nitrate in Sulfuric Acid.

Tetrahydroisoquinoline (21.5 g, 161 mmoles) was dissolved in concentrated sulfuric acid (80 ml) with cooling. Potassium nitrate (17.5 g, 173 mmoles) was added in small portions to the stirred solution whose temperature was kept below 5°. The reaction mixture was allowed to stand overnight at room temperature and then poured onto ice. The resulting solution was basified with aqueous ammonia and the products isolated by extraction with chloroform. The crude oil thus obtained was dissolved in ethanol (120 ml) and concentrated hydrochloric acid (20 ml) added. The precipitated hydrochloride salt of 7-nitrotetrahydroisoquinoline (52%) was recrystallised from methanol, mp 214-216°.

Anal. Calcd. for $C_9H_{11}ClN_2O_2$: C, 50.36; H, 5.17; N, 13.05. Found: C, 50.52; H, 5.24; N, 12.82.

The hydrochloride was converted to the *N*-acetyl derivative **2** as described in section (a).

2-Acetyl-5,7-dinitro-1,2,3,4-tetrahydroisoquinoline (**3**).

7-Nitrotetrahydroisoquinoline (1 g), liberated as an oil from the hydrochloride, was added with cooling to concentrated sulfuric acid (4 ml) and nitric acid (1 ml, d 1.35) then added dropwise to the stirred solution kept below 5°. The reaction mixture was allowed to stand overnight at room temperature, then poured onto ice, basified with aqueous ammonia and the crude product isolated by chloroform extraction. The material thus obtained was dissolved in ethanol (10 ml) and acetic anhydride (2 ml) added. After 3 hours the reaction mixture was evaporated *in vacuo*, the residue taken up in chloroform and washed successively with sodium carbonate solution and water. Evaporation gave an oil which crystallised from ethyl acetate to yield **3** (80%).

2-Acetyl-7-amino-1,2,3,4-tetrahydroisoquinoline (**4**).

The 7-nitro compound **2** (14 g, 68.6 mmoles) dissolved in ethanol (200 ml) was subjected to catalytic hydrogenation at 60 psi and room temperature for 24 hours in the presence of 10% palladium-on-charcoal (1 g). The filtered solution was then evaporated *in vacuo* to give an oil which was crystallised from ethyl acetate to yield **4**, mp 107-109°; ir: 3400, 3340, 1620 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.03 (s, 3H, $NCOCH_3$), 2.48-2.83 (m, 2H, H-4), 3.30-3.74 (m, 2H, H-3), 3.57 (s, 2H, exchangeable with deuterium oxide, NH_2), 4.30 and 4.42 (singlets, 2H, H-1), 6.22 (s, 1H, H-8), 6.30 (d, 1H, ArH, J = 8.0 Hz), 6.70 (d, 1H, ArH, J = 8.0 Hz) ppm.

Anal. Calcd. for $C_{11}H_{14}N_2O$: C, 69.45; H, 7.42; N, 14.73. Found; C, 69.63; H, 7.49; N, 14.65.

2-Acetyl-7-hydroxy-1,2,3,4-tetrahydroisoquinoline (**1**).

The amine **4** (9 g, 47 mmoles) was dissolved in a mixture of concentrated sulfuric acid (10 ml), water (20 ml) and ice (30 g). The mixture was stirred and a solution of sodium nitrite (8 g, 116 mmoles) in water (10 ml) was added dropwise over a period of 15 minutes while maintaining the temperature of the reaction mixture between −5 and 0°. The mixture was then kept *ca.* 0° for 4 hours to complete diazotisation before addition of urea to destroy excess nitrous acid. The filtered solution was added slowly to boiling 2*M* sulfuric acid (200 ml). This was then cooled and extracted with chloroform. The resulting extracts were washed with 10% aqueous sodium hydroxide to remove the phenolic product. These washings were subsequently acidified and the crude **1** recovered by chloroform extraction. Pure **1** (15%) was obtained by crystallisation from ethyl acetate, mp 149-151°; ir: 3250, 1640, 1580, 1530 cm^{-1}; ^{1}H nmr (deuteriochloroform): 2.18 (s, 3H, $NCOCH_3$), 2.72-2.95 (m, 2H, H-4), 3.56-3.81 (m, 2H, H-3), 4.54 and 4.68 (singlets, 2H, H-1), 6.72 (d, 1H, ArH, J = 9.2 Hz), 6.76 (s, 1H, H-8), 7.01 (d, 1H, ArH, J = 9.2 Hz) ppm.

Anal. Calcd. for $C_{11}H_{13}NO_2$: C, 69.09; H, 6.85; N, 7.33. Found: C, 69.42; H, 6.88; N, 7.42.

7-Methoxyisocarbostyril (**7**).

p-Methoxycinnamic acid (49.5 g, 278 mmoles) in toluene (200 ml) was heated to 80° and thionyl chloride (28.5 ml, 393 mmoles) added dropwise. The reaction mixture was kept at 80° for a further 3 hours and then evaporated *in vacuo* to give *p*-methoxycinnamoyl chloride. A solution of this in *m*-xylene (50 ml) was added slowly to a suspension of sodium azide (30 g, 462 mmoles) in *m*-xylene at 120° and the reaction mixture kept at

this temperature for a further 5 hours. The reaction mixture was then cooled, filtered and evaporated *in vacuo* to give *p*-methoxystyryl isocyanate (80%) as an oil; ir: 2250, 1600, 1490, 1250, 870, 840 cm^{-1}. This isocyanate (30 g) in *o*-dichlorobenzene (200 ml) containing a crystal of iodine was heated under reflux overnight. The solvent was then evaporated *in vacuo* to leave a brown residue which was triturated with acetonitrile to afford **7** (75%), mp 206-208° from methanol (lit [8] 207-207.5°); ir: 1650, 1480, 1390, 1300, 1090, 920, 900 cm^{-1}; ^1H nmr (hexadeuterioacetone): 3.94 (s, 3H, $-OCH_3$), 6.53 (d, 1H, -CH=, J = 7.3 Hz), 7.14 (d, 1H, -CH=, J = 7.3 Hz), 7.32 (dd, 1H, H-6, J = 8.6 and 2.6 Hz), 7.61 (d, 1H, H-5, J = 8.4 Hz), 7.76 (d, 1H, H-8, J = 2.8 Hz) ppm.

Anal. Calcd. for $C_{10}H_9NO_2$: C, 68.56; H, 5.18; N, 7.99. Found: C, 68.14; H, 5.17; N, 7.76.

Iodomethane (3 ml) was added dropwise to 7-methoxyisocarbostyril (1 g) and sodium hydroxide (0.5 g) in refluxing methanol (50 ml). After a further 6 hours heating under reflux the methanolic solution was decanted from precipitated sodium iodide and evaporated *in vacuo*. The residue was partitioned between chloroform and water, and the organic layer separated and evaporated. The crude product thus obtained was purified by chromatography over silica gel in chloroform to give the *N*-methyl derivative of **7** (90%), mp 101-103° from methanol; ir: 1645, 1610, 1255, 1110, 950, 855, 1040 cm^{-1}; ^1H nmr (deuteriochloroform): 3.58 (s, 3H, NCH_3), 3.90 (s, 3H, OCH_3), 6.42 (d, 1H, -CH=, J = 7.3 Hz), 6.93 (d, 1H, -CH=, J = 7.3 Hz), 7.21 (dd, 1H, ArH, J = 8.7 and 2.7 Hz), 7.40 (d, 1H, ArH, J = 8.7 Hz), 7.81 (d, 1H, ArH, J = 2.7 Hz) ppm; ms: m/e 189 (M^+, 30%), 175 (8%), 162 (60%), 147 (30%), 118 (100%).

Anal. Calcd. for $C_{11}H_{11}NO_2$: C, 69.81; H, 5.83; N, 7.45. Found: C, 70.20; H, 6.14; N, 7.45.

7-Methoxy-3,4-dihydroisocarbostyril (**9**).

7-Methoxyisocarbostyril (28.5 g, 163 mmoles) in ethanol (300 ml) was hydrogenated at 60 psi and 80° in the presence of 10% palladium on charcoal catalyst (1 g) for 48 hours. The filtered solution was evaporated *in vacuo* to give **9**, mp 86-88° from methanol (90%); ir: 1630, 1550, 1380, 1270, 1130, 820 cm^{-1}; ^1H nmr (deuteriochloroform): 2.90 (t, 2H, H-4, J = 6.8 Hz), 3.49 (t, 2H, H-3, J = 6.8 Hz), 3.79 (s, 3H, OCH_3), 7.02 (dd, 1H, ArH, J = 8.7 and 2.7 Hz), 7.23 (d, 1H, ArH, J = 8.7 Hz), 7.53 (d, 1H, ArH, J = 2.7 Hz) ppm; ms: m/e 177 (M^+, 55%), 148 (54% M-CH_2NH), 120 (100%, M-CH_2NHCO).

Anal. Calcd. for $C_{10}H_{11}NO_2$: C, 67.75; H, 6.23; N, 7.92. Found: C, 67.78; H, 6.21; N, 7.92.

7-Methoxy-1,2,3,4-tetrahydroisoquinoline (**10**).

A solution of the dihydroisocarbostyril **9** (15.9 g, 90 mmoles) in tetrahydrofuran (100 ml) was added slowly to a suspension of lithium aluminium hydride (2.7 g, 71 mmoles) and the reaction mixture was refluxed subsequently for 24 hours. The solvent was then partially evaporated and 20% aqueous sodium hydroxide added, followed by water (300 ml). The product **10** was isolated by ether extraction as an oil (84%); ir: 3250 cm^{-1}; ^1H nmr (deuteriochloroform): 2.45 (t, 2H, H-4, J = 7.0 Hz), 2.78 (t, 2H, H-3, J = 7.0 Hz), 3.65 (s, 3H, OCH_3), 4.55 (s, 2H, H-1), 6.48 (dd, 1H, ArH, J = 8.7 and 2.8 Hz), 6.65 (d, 1H, ArH, J = 8.7 Hz) ppm; ms: m/e 163 (M^+, 40%), 162 (25%), 161 (28%), 159 (20%), 134 (100%, M-CH_2NH).

The compound **10** was converted to the *N*-acetyl derivative by treatment with acetic anhydride in ethanol, mp 57-59° from ethanol; ir: 1650, 1580, 1450, 1390, 1030, 810 cm^{-1}; ^1H nmr (deuteriochloroform): 2.09 (s, 3H, $NCOCH_3$), 2.45-2.85 (m, 2H, H-4), 3.35-3.80 (m, 2H, H-3), 3.68 (s, 3H, OCH_3), 4.55 (s, 2H, H-1), 6.68 (s, 1H, ArH), 6.73 (d, 1H, ArH, J = 8.7 Hz), 7.05 (d, 1H, ArH, J = 8.7 Hz) ppm.

Anal. Calcd. for $C_{12}H_{15}NO_2$: C, 70.24; H, 7.31; N, 6.83. Found: C, 70.15; H, 7.35; N, 6.85.

7-Acetoxy-2-acetyl-1,2,3,4-tetrahydroisoquinoline **6** and Conversion to **1**.

7-Methoxytetrahydroisoquinoline (19.5 g, 120 mmoles) in 48% hydrobromic acid (200 ml) was heated under reflux for 12 hours and then evaporated *in vacuo*. The resulting solid was dissolved in pyridine (200 ml), acetic anhydride (20 ml) added and the resulting solution refluxed for 6 hours. Most of the volatile solvents were then evaporated *in vacuo* and the residue partitioned between chloroform and water. The organic extract was washed with 10% sodium carbonate solution and water prior to drying over sodium sulfate and subsequent evaporation. The resulting oil was chromatographed over silica gel in chloroform to give **6** (65%) as an oil; ir: 1720, 1650, 1590, 1450, 1040, 800 cm^{-1}; ^1H nmr (deuteriochloroform): 2.16 (s, 3H, $NCOCH_3$), 2.28 (s, 3H, $OCOCH_3$), 2.64-3.0 (m, 2H, H-4), 3.52-3.85 (m, 2H, H-3), 4.59 and 4.70 (singlets, 2H, H-1), 6.8-7.3 (m, 3H, ArH).

The diacetyl compound **6** (12.5 g, 54 mmoles) was dissolved in Analar methanol (100 ml) and moist activated zinc [6] (20 g) added. The reaction mixture was stirred at room temperature for 6 hours, then filtered through Celite and the methanol evaporated *in vacuo*. The residue was partitioned between ether and 10% hydrochloric acid. The ether extract was washed with water, dried over sodium sulfate and evaporated to yield **1** (90%).

Oxidation of **1**.

2-Acetyl-7-hydroxytetrahydroisoquinoline **1** (2.5 g, 13 mmoles) and sodium carbonate (10.6 g) in water (500 ml) were cooled to 0-10° and potassium ferricyanide (13.97 g, 42.4 mmoles) in water (100 ml) added with stirring over 1 hour. After a further 3 hours stirring the reaction mixture was extracted with ether and the extracts washed with 5% sodium hydroxide solution and water. Evaporation of the ether solution gave a small quantity (*ca.* 20 mg) of an apparently homogeneous material (tlc); ^1H nmr (deuteriochloroform): 2.21 (s, 6H, 2 × $NCOCH_3$), 2.86-3.19 (m, 8H, 4 × CH_2), 5.29 (s, 2H, 2 × OCH), 6.95 (d, 2H, 2 × ArH, J = 8.7 Hz), 7.37 (d, 1H, ArH, J = 8.7 Hz); ms: m/e 376 (M^+, 100%), 345 (45%), 310 (25%).

Anal. Calcd. for $C_{22}H_{20}N_2O_4$: C, 70.21; H, 5.32; N, 7.45. Found: C, 69.93; H, 5.44; N, 7.39.

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