Reaction of *N*-Nitroaryl-1,2,3,4-tetrahydroisoquinoline Derivatives with Oxygen

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Heating *N*-4'-methyl-2'-nitrophenyl-1,2,3,4-tetrahydroisoquinoline (**1**) in the presence of oxygen gave both products derived from cleavage of the C8a-Cl bond and oxidation at the 1-position. Under similar conditions *N*-4'-nitrophenyl-1,2,3,4-tetrahydroisoquinoline (**4**) gave only the oxidation product.

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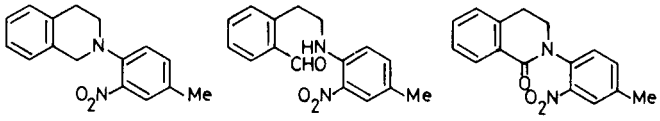
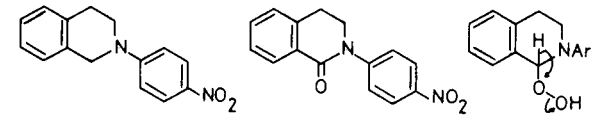
When 1,2,3,4-tetrahydroisoquinoline was heated [100°, dimethyl sulphoxide (DMSO), 2 hours] with 4-methyl-2-nitrofluorobenzene, *N*-4'-methyl-2'-nitrophenyl-1,2,3,4-tetrahydroisoquinoline (**1**) (93% yield) was isolated as expected. The formation of two other products was also observed during this reaction (by tlc analysis) and these products were assumed to have been formed by further reaction of compound **1** under the reaction conditions. This assumption was confirmed by heating compound **1** in DMSO solution (100°, 78 hours) which afforded, after chromatography, aldehyde **2** (38% yield) and lactam **3** (12% yield) together with unreacted compound **1** (38% yield). When aldehyde **2** was heated under the reaction conditions no lactam **3** was detected and aldehyde **2** was recovered (80% yield) indicating that lactam **3** is not formed from aldehyde (**2**) by an oxidative process and that compounds **2** and **3** were formed in competing reactions. When the reaction time was increased to 4.5 days, the yield of product **2** from compound **1** was reduced to 23%.



1 2 3

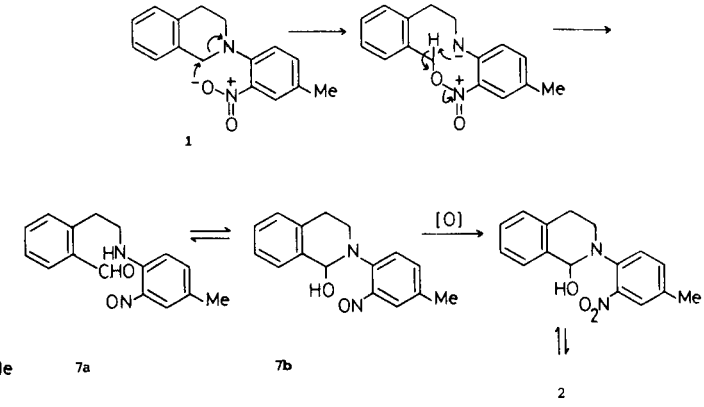
DMSO and/or oxygen were recognised as possible oxidising agents in this reaction and the effect of DMSO and oxygen on the course of the reaction were therefore investigated. Thus, compound **1** was heated in dimethylformamide (DMF) solution (100°, 75 hours) giving aldehyde **2** (16% yield) and lactam **3** (7% yield) together with compound **1** (39% yield) and DMSO was therefore excluded as an oxidant. When compound **1** was heated in DMSO solution under an atmosphere of nitrogen, no aldehyde **2** or lactam **3** were formed and compound **1** (50% yield) was recovered and the requirement of oxygen for the formation of products **2** and **3** was therefore established.

In order to gain further information about this reaction, *N*-4'-nitrophenyl-1,2,3,4-tetrahydroisoquinoline **4** was similarly heated in DMSO solution (100°, 80 hours) giving, after chromatography, lactam **5** (30% yield) together with unreacted compound **4** (41% yield). No aldehyde product was isolated in this reaction.



4 5 6

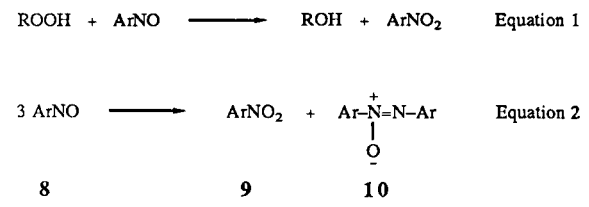
Scheme



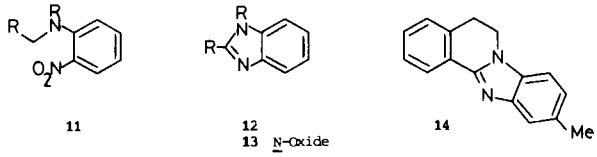
The formation of lactams **3** and **5** in the reactions described above can be rationalised as follows. Reaction of compounds **1** or **4** at the 1-position with molecular oxygen would afford the hydroperoxide derivative **6** from which lactams **3** and **5** may be formed by loss of water [arrows, formula **6**].

A tentative mechanism which accounts for the formation of aldehyde **2** from compound **1** and the absence of any aldehyde product from compound **4** is depicted in the Scheme. This reaction involves participation of the appositely located nitro-group of compound **1** in a ring opening step. The resulting nitroso group in intermediate **7a** ⇌ **7b** is then oxidised by hydroperoxide **6** giving the product **2**. The oxidation of nitroso groups by a variety of reagents [1] including peroxides (Equation 1) [2] is well established. The thermal reaction (70-100°, cyclohexane solution) of nitroso compounds **8** (Equation 2) giving the nitro- and

azoxy-compounds **9** and **10** respectively has been investigated [3]. In our case no compound which corresponds to the azoxy derivative **10** has been isolated which precludes formation of product **2** from intermediate **7a** ⇌ **7b** by a similar reaction.



N,N-Disubstituted 2-nitroaryl compounds represented by the general formula (**11**) can be cyclised under reductive conditions or by heating giving the corresponding benzimidazole derivatives **12** or their *N*-oxides **13** (the *t*-amino effect [4]). Compound **1** is not participating in such a reaction because no product **14** which would be expected from the *t*-amino effect was isolated. When compound **1** was reduced with titanium trichloride in the presence of hydrochloric acid, compound **14** was produced (39% yield) by the *t*-amino effect.



11 12 13 N-Oxide 14

EXPERIMENTAL

Melting points are uncorrected. Proton nmr spectra (90 MHz) were determined in deuteriochloroform solution using tetramethylsilane as an internal standard. Infra-red spectra were determined as potassium bromide discs unless otherwise stated.

N-4′-Methyl-2′-nitrophenyl-1,2,3,4-tetrahydroisoquinoline (**1**).

A mixture of 1,2,3,4-tetrahydroisoquinoline (6.65 g), 4-methyl-2-nitrofluorobenzene (7.7 g) and potassium carbonate (10.0 g) in DMSO (20 ml) was heated (2 hours) at 100° (oil-bath temperature) and then allowed to cool to room temperature. The mixture was poured onto water and the resulting orange precipitate of *N*-4′-methyl-2′-nitrophenyl-1,2,3,4-tetrahydroisoquinoline (**1**) (12.4 g, 93%) mp 82-83° (from ethanol) was collected, washed with water and dried *in vacuo*; ir: ν max 1620, 1525 and 1345 cm^{-1}; ^1H nmr: δ 7.60 (1H, s, Ar-H), 7.20 (1H, s, Ar-H), 7.15 (5H, broad s, Ar-*H*), 4.30 (2H, s, $>CH_2$), 3.40 (2H, t, J = 6 Hz, $-CH_2CH_2-$), 2.95 (2H, t, J = 6 Hz, $-CH_2CH_2-$) and 2.35 (3H, s, $-CH_3$).

Anal. Calcd. for $C_{16}H_{16}N_2O_2$: C, 71.6; H, 6.0; N, 10.4. Found: C, 71.3; H, 6.1; N, 10.5.

Reactions of Compounds **1**, **2** and **4**.

General Method.

A solution of compounds **1**, **2** or **4** in the appropriate solvent was heated (100°, oil-bath temperature) for the specified period in air or under an atmosphere of nitrogen. The mixture was allowed to cool to room temperature and then poured into water, extracted with dichloromethane or ether, washed with water and dried (magnesium sulphate). The solvents were evaporated under reduced pressure and the residue was fractionated by column chromatography (silica gel, eluent dichloromethane) giving the products. All products were recrystallised from ethanol. By this method the following transformations were achieved:

(a) Compound **1** (2.68 g) in DMSO (20 ml) (78 hours) in air gave recovered compound **1** (1.02 g, 38%), *N*-[2-(2′-formyl)phenyl]-ethyl-4-methyl-2-nitroaniline **2** (1.08 g, 38%), mp 98.5-100.5° and *N*-(4′-methyl-2′-nitrophenyl)-3,4-dihydroisoquinolin-1-one **3** (0.34 g, 12%), mp 149.5-151°. In a similar experiment (4.5 days) the yield of compound **2** was 23%.

Compound **2** had ir: ν max 3380 (>NH) and 1680 (C=O) cm^{-1}; ^1H nmr: δ 10.15 (1H, s, -C*H*O), 7.95-6.85 (7H, m, Ar-*H*), 3.50 (4H, m, $-CH_2-CH_2-$) and 2.25 (3H, s, $-CH_3$).

Anal. Calcd. for $C_{16}H_{16}N_2O_3$: C, 67.6; H, 5.7; N, 9.9. Found: C, 67.6; H, 5.6; N, 9.9.

Compound **3** had ir: ν max 1670 (C=O) and 1530 cm^{-1}; ^1H nmr: δ 8.10-7.25 (7H, m, Ar-*H*), 4.00 (2H, t, J = 6 Hz, $-CH_2CH_2-$), 3.30 had (2H, broad t, $-CH_2CH_2-$) and 2.45 (3H, s, $-CH_3$).

Anal. Calcd. for $C_{16}H_{14}N_2O_3$: C, 68.1; H, 5.0; N, 9.9. Found: C, 68.3; H, 5.0; N, 9.9.

(b) Compound **1** (1.5 g) in DMF (*ca* 10 ml) (75 hours) in air gave recovered compound **1** (0.59 g, 39%), compound **2** (0.25 g, 16%) and compound **3** (0.11 g, 7%).

(c) Compound **1** (1.0 g) in DMSO (*ca* 10 ml) (78 hours) under an atmosphere of nitrogen gave only recovered compound **1** (0.50 g, 50%). Compounds **2** and **3** could not be detected in this reaction by tlc analysis.

(d) Compound **4** [5] (1.5 g) in DMSO (15 ml) (80 hours) in air gave unreacted compound **5** (0.61 g, 41%) and *N*-(4-nitrophenyl)-3,4-dihydroisoquinolin-1-one (**5**) (0.47 g, 30%), mp 154-155°; ir: ν max 1650 (C=O), 1515 and 1330 cm^{-1}; ^1H nmr: δ 8.25-7.25 (8H, m, Ar-*H*), 4.05 (2H, t, J = 6 Hz, $-CH_2CH_2-$) and 3.15 (2H, t, J = 6 Hz, $-CH_2CH_2-$).

Anal. Calcd. for $C_{15}H_{12}N_2O_3$: C, 67.2; H, 4.5; N, 10.4. Found: C, 67.2; H, 4.5; N, 10.4.

(e) Compound **2** (200 mg) in DMSO (5 ml) (96 hours) under an atmosphere of nitrogen gave only recovered compound **2** (160 mg, 80%).

5,6-Dihydro-10-methylbenzimidazo[2,1-*a*]isoquinoline (**14**).

To a stirred solution of compound **1** (1.0 g) in concentrated hydrochloric acid (30 ml) at 80° under an atmosphere of nitrogen was added a 30% solution of titanium trichloride in concentrated hydrochloric acid (*ca* 7 ml) over 1.5 hours until a purple colour persisted. The mixture was allowed to cool to room temperature, poured onto cold dilute sodium hydroxide solution and extracted with ether. The organic extracts were washed with water, dried (magnesium sulphate) and evaporated under reduced pressure. The residue was fractionated by column chromatography [silica gel: eluent petroleum ether bp 40/60°: ethyl acetate (3:2)] giving compound **14** (0.34 g, 39%) as a cream solid, mp 177-178°; ir: ν max 1495, 1455 and 800 cm^{-1}; ^1H nmr: δ 8.25 (1H, m, Ar-*H*), 7.60 (1H, m, Ar-*H*), 7.45-7.00 (5H, m, Ar-*H*), 4.25 (2H, t, J = 7 Hz, $-CH_2CH_2-$), 3.20 (2H, t, J = 7 Hz, $-CH_2CH_2-$) and 2.45 (3H, s, $-CH_3$).

Anal. Calcd. for $C_{16}H_{14}N_2$: C, 81.7; H, 6.0; N, 11.8. Found: C, 82.0; H, 6.0; N, 12.0.

Acknowledgement.

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