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An unexpected ring contraction of two nitroaryl pro-drugs: conversion of *N*-(nitroaryl)-3-chloropiperidine derivatives into *N*-(nitroaryl)-2-chloromethylpyrrolidines

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ABSTRACT

Treatment of the *N*-nitroaryl-3-hydroxypiperidine derivatives **12** and **13** with thionyl chloride afforded the corresponding *N*-aryl-2-chloromethylpyrrolidines **5** and **15** via a ring-contraction process involving an intermediate aziridinium ion.

Many nitroaromatic pro-drugs have been designed as potential substrates for the enzyme DT-diaphorase, also known as NAD(P)H: quinone oxidoreductase 1 (NQO1).[1] Elevated levels of NQO1 are often found in tumour tissue making this enzyme an attractive target for nitroaromatic pro-drug therapies.[2] CB-1954 (**1**) (Fig. 1) was shown to be an effective anti-cancer agent against rat Walker 256 carcinomas,[3] but unfortunately, human cell lines were unresponsive; this was attributed to a change in the amino acid residue 104 (tyrosine in the rat enzyme and glutamine in the human enzyme). In the presence of either of the cofactors NADH or NADPH, NQO1 catalyses the bioreduction of **1** to produce the 4-hydroxylamine derivative **2** which, after reaction with acetyl CoA, generates compound **3**, capable of producing lethal DNA–DNA interstrand crosslinks.[4] However, **1** is reduced more

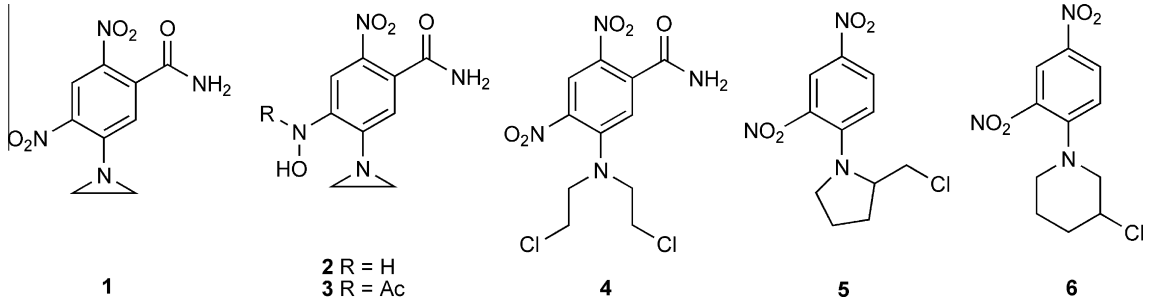

Figure 1. Nitroaryl pro-drug structures.

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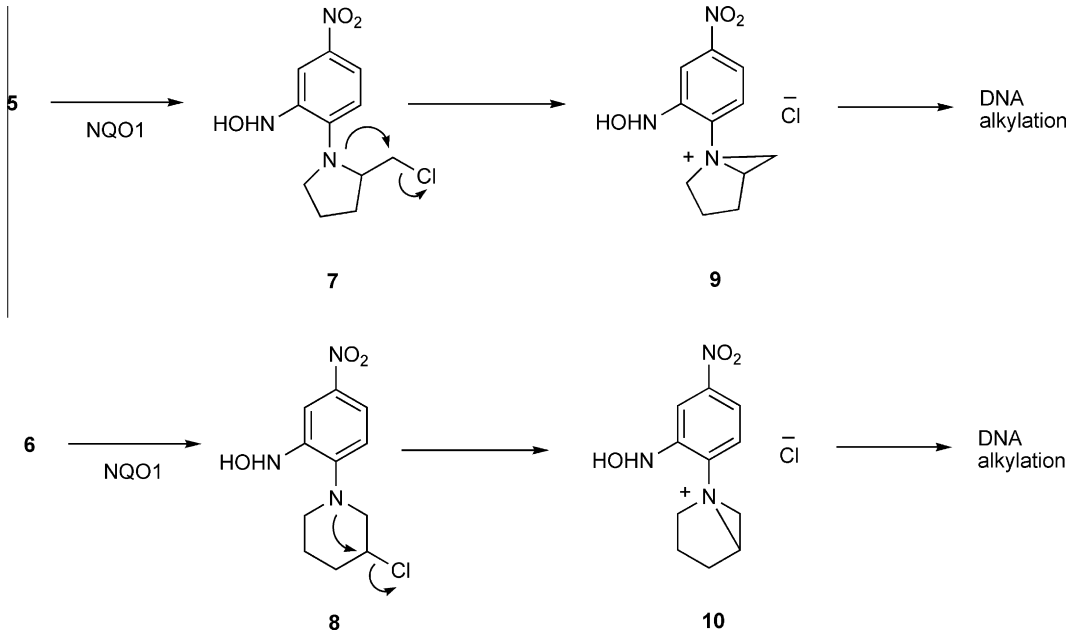
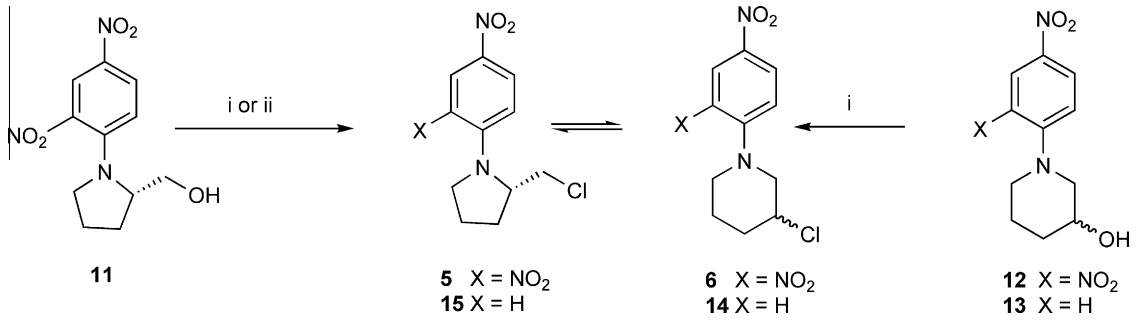


Scheme 1. Potential mechanism for DNA alkylation by bioreduction of **5** and **6**.



Scheme 2. Formation of pyrrolidines **5** and **15** from **11** and piperidines **12** and **13**. (i) $SOCl_2$, CH_2Cl_2, reflux; (ii) cyanuric chloride, DMF, rt.

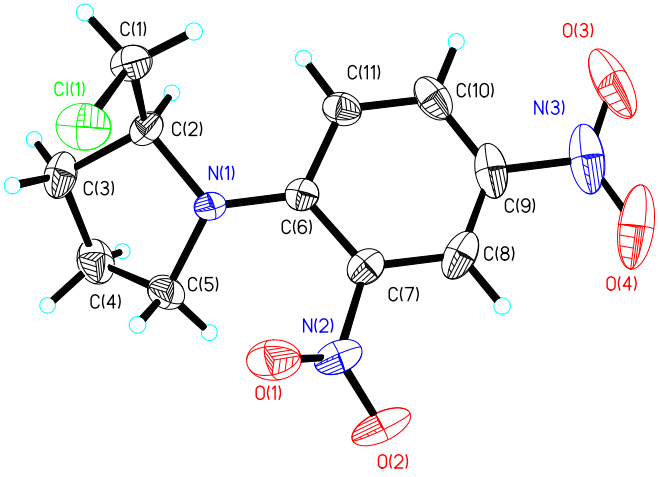


Figure 2. X-ray structure of compound **5**. Ellipsoids are shown at the 50% probability level.

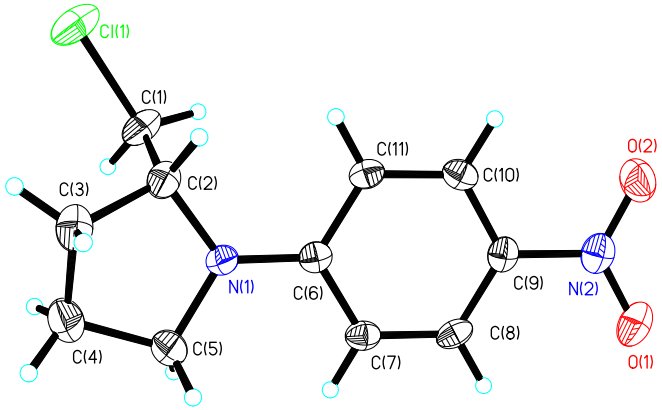
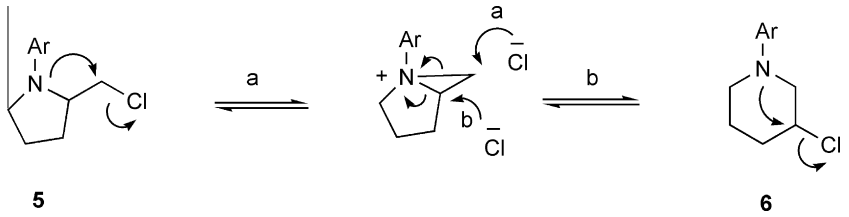


Figure 3. X-ray structure of compound **15**. Ellipsoids are shown at the 50% probability level.

effectively by *Escherichia coli* nitroreductase (NR) and this observation has generated interest in activating **1** in tumours by using either antibody directed enzyme pro-drug therapy (ADEPT) or virus/gene-directed enzyme pro-drug therapy (VDEPT/GDEPT).[5] The structurally related dinitrobenzamide mustard, SN-23862 (**4**), is also a poor substrate for NQO1, but has been identified as a better substrate for NR than **1**.[6] We have been interested in developing new NQO1/NR substrates, and hence potential anti-tumour agents



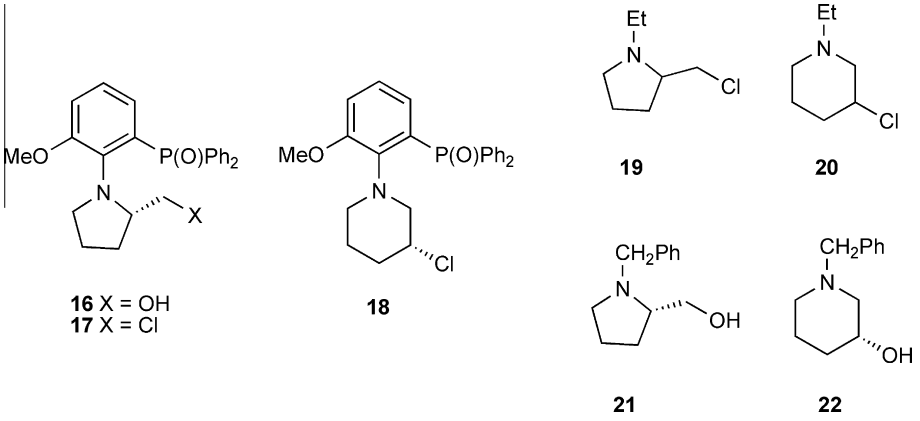
Scheme 3. Interconversion of compounds **5** and **6** via an aziridinium intermediate.

that are structurally related to **1** and **4**. To this end the dinitrobenzenes **5** and **6** were chosen as potential substrate candidates. It was anticipated that NQO1-mediated bioreduction of either the 2- or 4-nitro-group in these compounds would generate the corresponding hydroxylamine derivatives **7** and **8**, and the resulting change in the electronic character of the aryl group would promote the formation of aziridinium ions **9** and **10**, respectively (Scheme 1). These highly reactive aziridinium species **9** and **10** might then be capable of cross-linking DNA in a similar fashion to the parent CB-1954 (**1**) agent.

(*S*)-Prolinol was treated with 2,4-dinitrofluorobenzene under basic conditions yielding the N-arylated product **11** in 79% yield (Scheme 2).[7] Racemic 3-hydroxypiperidine was reacted with 2,4-dinitrofluorobenzene under basic conditions (K_2CO_3, DMSO, room temperature, 6 h) producing compound **12** in 91% yield. Treatment of alcohol **11** with thionyl chloride in boiling dichloromethane gave a mixture of products (66:34; 81%) that was initially assumed to comprise the isomers **5** and **6**. As a consequence of the similar connectivity [$NCHCH_2Cl$ vs NCH_2CHCl] for the **5**/**6** isomeric pair, the assignment of structures to each product by NMR spectroscopy by either prediction of coupling constants from the ^1H spectra or chemical shift prediction from the ^{13}C spectra was inconclusive. The ^1H NMR spectrum (in $CDCl_3$) of the mixture showed two multiplets at ca. 4.32 and 4.12 ppm which were attributed to the >CH– protons of compounds **5**/**6**. However, a single chlorinated product (61%) showing a multiplet at 4.32 ppm ($CDCl_3$) in its ^1H NMR spectrum was obtained by treating compound **11** with cyanuric chloride and DMF.[8,9] The structure of this solid product was elucidated by an X-ray crystallographic study which indicated the presence of the pyrrolidine ring (Fig. 2).[10] Treatment of alcohol **12** with thionyl chloride in boiling dichloromethane solution also afforded racemic compound **5** (80%)[9] whose ^1H NMR spectrum was identical with that obtained from the reaction of **11** with cyanuric chloride. In view of these results, we were also interested in examining the chlorination of the mono-nitro derivative **13**.[11] Treatment of **13** with thionyl chloride similarly afforded the racemic ring-contracted product **15** (42%)[12] whose structure was also confirmed by X-ray crystallography (Fig. 3).[10] It is evident that the chlorinated piperidine derivatives **6** and **14** undergo an intramolecular ring-contraction to yield the corresponding pyrrolidines **5** and **15**, respectively.

The expansion/contraction process can be explained in terms of an intermediate aziridinium ion species as depicted in Scheme 3. To our knowledge, there are relatively few examples of ring expansion/contractions of N-arylated compounds. Mino et al. have described the reaction of the prolinol derivative **16** with thionyl chloride and triethylamine in $CHCl_3$ at room temperature which yielded a mixture of compound **17** (31%) and the ring-expanded product **18** (51%).[13] Heating compound **17** in $CHCl_3$ afforded piperidine **18** in quantitative yield. In contrast, the ring expansion/contraction of N-alkylated derivatives has been known for a long time. Fuson and Zirkle described the ring expansion of 1-ethyl-2-chloromethylpyrrolidine (**19**) to give 1-ethyl-3-chloropiperidine (**20**) upon treatment of the hydrochloride salt with alkali.[14] Hammer et al. found that the hydrochloride salts of compounds **19** and **20** afforded either five- or six-membered ring products when treated with a base and a nucleophile.[15] Cossy et al. have reacted *N*-benzyl prolinol (**21**) with firstly a mixture of trifluoroacetic anhydride and triethylamine, followed by aqueous NaOH to obtain *N*-benzyl-3-hydroxypiperidine (**22**) (63%).[16] Related ring-expansions have been exploited in natural product synthesis.[17]

In view of the electron-deficient nature of the *N*-nitroaryl substituents in **6** and **14** this ring contraction process was unexpected and the examples reported here are, to our knowledge, unprecedented.



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Supplementary data

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.tetlet.2010.05.095.

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9. Synthesis of compound **5**. Method A: Cyanuric chloride (0.92 g, 5.00 mmol) was added to DMF (1 mL) at room temperature. After the formation of a pale yellow solid (3 h), CH_2Cl_2 (5 mL) was added, followed by compound **11** (0.23 g, 0.86 mmol) in CH_2Cl_2 (5 mL) and the resulting mixture stirred at room temperature (20 h). H_2O (20 mL) was added to quench the reaction and the organic phase was separated, washed with a saturated solution of Na_2CO_3 (20 mL), followed by 1 M HCl (10 mL) and finally brine (10 mL). The organic layer was dried ($MgSO_4$) and the solvent evaporated giving the crude chlorinated compound **5** as a brown oil (0.21 g, 85%). Purification by column chromatography (silica gel; EtOAc/hexane; 1:1; R_f 0.82) gave compound **5** as a yellow oil (0.15 g, 61%) which was crystallised from hexane/CH_2Cl_2, mp 77–78 °C. ^{1}H NMR (270 MHz, $CDCl_3$): δ 1.78–1.96 (m, 1H, CH_2), 2.01–2.18 (m, 2H, CH_2), 2.39–2.52 (m, 1H, CH_2), 2.94–3.05 (m, 1H, CH_2), 3.49–3.66 (m, 2H, CH_2), 3.70 (dd, 1H, CH_2, J = 11.63 and 2.97 Hz), 4.32 (ddd, 1H, CH, J = 2.72, 7.17 and 14.10 Hz), 7.04 (d, 1H, J = 9.40 Hz), 8.25 (dd, 1H, J = 9.40 and 2.72 Hz), 8.70 (d, 1H, J = 2.72 Hz); ^{13}C NMR (68 MHz, $CDCl_3$): δ 24.7, 30.0, 44.7, 53.3, 60.2, 116.2, 124.1, 127.9, 136.5, 136.8, 145.2; HRMS (EI) m/z: $C_{11}H_{12}ClN_3O_4$ $[M]^+$: calcd 285.0511, measured 285.0507. Method B: $SOCl_2$ (1 mL) was added to a solution of compound **12** (0.36 g, 1.347 mmol) in CH_2Cl_2 (15 mL). The mixture was heated at reflux (15 h), allowed to cool to room temperature, and then evaporated. The residue was purified by column chromatography giving racemic compound **5** (0.31 g, 80%).
10. X-ray data are given in the Supplementary data. Crystallographic data have been deposited with the Cambridge Crystallographic Data Centre CCDC 767027 (compound **5**) and CCDC 767028 (compound **15**). Copies of the data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [Fax: (international) +44-1223/336-033; e-mail: deposit@ccdc.cam.ac.uk].
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