Potentially Carcinogenic Cyclopenta[*a*]phenanthrenes. Part 12.[1] Synthesis of metabolites of the Carcinogen 16,17-Dihydro-11-methoxy-15*H*-cyclopenta[*a*]-phenanthrene

J. Chem. Research (S), 1998, 692–693
J. Chem. Research (M), 1998, 2901–2911

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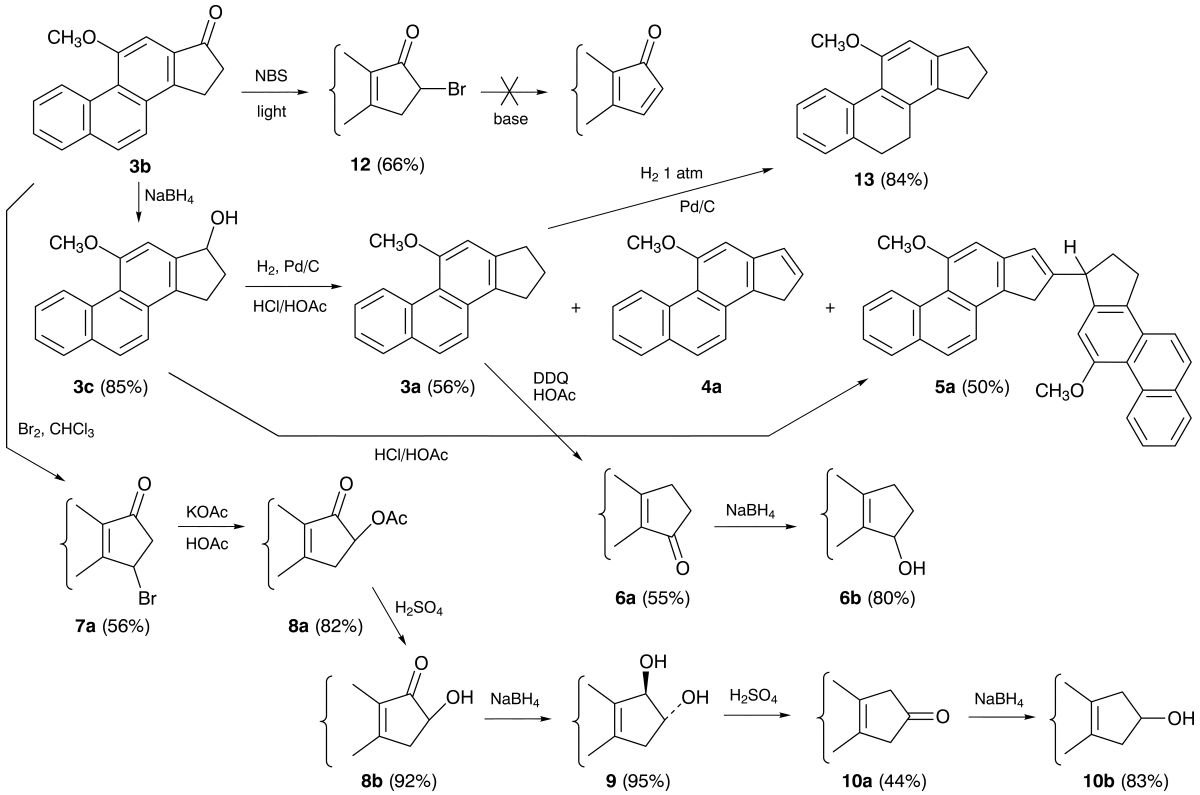
Starting with 15,16-dihydro-11-methoxycyclopenta[*a*]phenanthren-17-one, the isomeric 15- and 16-keto analogues have been synthesised along with all three isomeric secondary alcohols, the *trans*-16,17-diol and a number of other derivatives, some of which are metabolites of the title compound.

In the cyclopenta[*a*]phenanthrene series carcinogenicity is induced by the presence of a small electron-releasing group at C-11 in the bay-region,[2,3] and is greatly enhanced by further unsaturation in the five-membered ring. Thus the 11-methyl-17-ketone is a carcinogen with potency similar to that of the classic polycyclic aromatic hydrocarbon benzo[*a*]pyrene in the mouse,[4] whereas the 11-methyl hydrocarbon lacking unsaturation in this ring is only very weakly active.[5] Not unexpectedly the 11-methoxy-17-ketone **3b** is also a strong carcinogen,[2] but here there is a difference because the 11-methoxy hydrocarbon **3a** is almost equally active.[6] To understand the reason for this apparent anomaly we are studying the *in vitro* metabolism of this compound, and it is in this connection that the synthetic work described here has been undertaken, adapting methods previously established in this series for introducing oxygen at the three isomeric positions in the five-membered ring as shown in the flow diagram below.

Reduction of the known carcinogenic 11-methoxy-17-ketone **3b** with sodium tetrahydroborate gave the 17-ol **3c**, hydrogenolysis of which under acidic conditions led to the title 11-methoxy hydrocarbon **3a** together with smaller amounts of the corresponding 16,17-ene **4a** and dimer **5a**. The latter compound was also formed in 50% yield simply by treating the 17-ol **3c** with acid. The mixture of **3a** and **4a** was difficult to separate and attempts to hydrogenate it over palladium on charcoal at atmospheric pressure to obtain pure **3a** led unexpectedly, to the 6,7-dihydro derivative **13**. With both the unsubstituted and 11-methyl hydrocarbons, hydrogen (4 atm) is required to effect similar 6,7-saturations.[7] Free radical bromination[8] of the 11-methoxy-17-ketone **3b** by exposure to visible light in the presence of *N*-bromosuccinimide gave the 16-bromide **12** in high yield. However, this bromide was found to be inert to bases, whereas the analogous 16-bromides of the unsubstituted- and 11-methyl-17-ketones are readily dehydrobrominated[9]



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with triethylamine under mild conditions. These differences serve to emphasise the marked influence exerted by the methoxy substituent on the reactions of these compounds.

Oxidation of the 11-methoxy hydrocarbon **3a** with 2,3-dichloro-4,5-dicyanobenzoquinone in hot aqueous acetic acid gave the 15-ketone **6a** with no evidence of attack at the isomeric benzylic 17-position. Reduction with sodium tetrahydroborate then afforded the 15-ol **6b**. Electrophilic bromination of the 11-methoxy-17-ketone **3b** with elementary bromine in chloroform occurred readily to form, mainly, the 15-bromide **7a**. On being heated with potassium acetate in acetic acid the latter was smoothly converted into the 16-acetate **8a**, presumably by nucleophilic attack of acetate on the enol at C-16 with expulsion of bromide from C-15, as proposed[8] for the similar reaction with 15-bromo-15,16-dihydro-11-methylcyclopenta[*a*]phenanthren-17-one. After acid hydrolysis to the 16-hydroxy-17-ketone **8b**, reduction of the latter with sodium tetrahydroborate gave the *trans*-16,17-diol **9** which on being heated with aqueous sulfuric acid underwent dehydration to the 16-ketone **10a**. Reduction as before with sodium tetrahydroborate then yielded the 16-alcohol **10b**. New compounds were fully characterised by ultraviolet and proton NMR spectroscopy, and by mass spectrometry as well as elementary analysis, all reported in detail in the full text paper.

Techniques used: UV, IR, ^{1}H NMR and mass spectrometry

References: 11

Table 1: ^{1}H NMR chemical shifts (δ) and coupling constants (Hz) of ring-D protons in 15-bromo and 16-acetoxy-17-ketones

Table 2: Ions of mass >150 in the low resolution mass spectra of 16,17-dihydro-11-methoxy-15*H*-cyclopenta[*a*]phenanthrene and some of its derivatives

Received, 20th July 1998; Accepted, 21st July 1998
Paper E/8/05641B

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