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A NEW SYNTHESIS OF CYCLOPENTA[a]PHENANTHRENE AND ITS CARCINOGENIC DERIVATIVES

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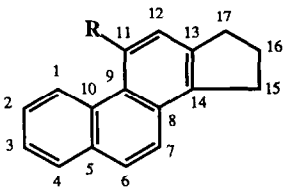
Summary: A novel synthesis of cyclopenta[a]phenanthrene and its carcinogenic 11-methyl and 17-keto derivatives is described.

Cyclopenta[a]phenanthrenes are widely distributed in petroleum, coal, mineral oils, lake sediments, and other natural environments[1-4] where they are thought to arise from sterols by microbiological dehydrogenation.[3,4] While 16,17-dihydro-15H-cyclopenta[a]phenanthrene (**1a**) and its 17-keto analog (**2a**) are inactive as carcinogens, the 11-methyl derivative (**1a**) is weakly active, and the 11-methyl-17-keto derivative (**2b**) is a relatively potent carcinogen in mice.[4-7] Biological investigations of the cyclopenta[a]phenanthrenes have been hampered by their unavailability except through tedious multistep syntheses.[4]



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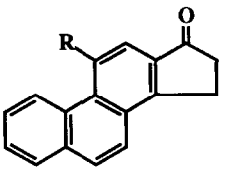

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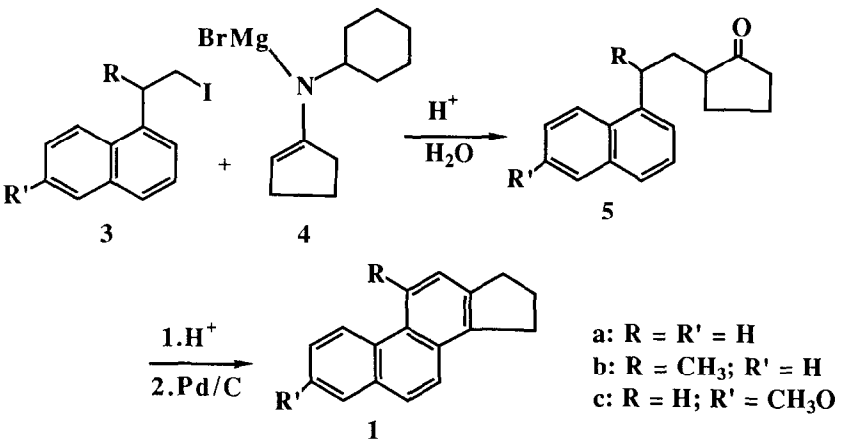
a: R = H; b: R = CH_3

We now report a novel synthesis of molecules of this class which provides good yields in relatively few steps. The method is also potentially adaptable to the preparation of the biologically active metabolites of the cyclopenta[a]phenanthrenes.

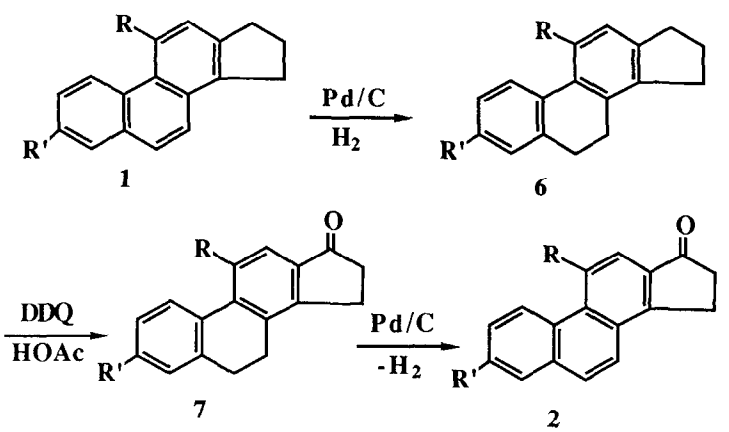
The synthetic route to the parent hydrocarbon **1a** is outlined in Chart 1. Reaction of 2-(1-naphthyl)ethyl iodide (**4a**)[8] with the bromomagnesium salt of N-cyclopentylidenecyclohexylimine (**5a**) followed by acidic hydrolysis of the resulting adduct affords smoothly 2-[2-(1-naphthyl)-ethyl] cyclopentanone (**6a**). Cyclization of **6a** in polyphosphoric acid furnishes 11,12,16,17-tetrahydro-15H-cyclopenta[a]phenanthrene (**7a**) accompanied by the products of acidic disproportionation (shown by NMR and TLC).[9] Dehydrogenation of the mixture over a 10% Pd/charcoal catalyst gives **1a** as a crystalline solid, mp 134-135°C (lit.[10] 134-135°C). The NMR spectrum of **1a** is also fully consistent with this assignment. Excellent yields are obtained in both the initial alkylation and hydrolysis steps (96%) as well as in the subsequent cyclization and dehydrogenation steps (85%).

Chart I



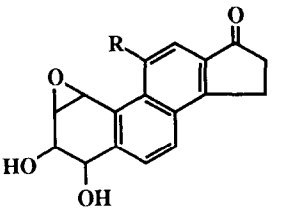
While direct oxidation of **1a** is a potentially attractive synthetic route to the 17-keto derivative, 16,17-dihydro-15H-cyclopenta[a]phenanthrene (**2a**), an earlier report by Butenandt et al.[11] that oxidation of **1a** with chromic acid affords the 15-keto derivative is discouraging. However, in our hands, oxidation of **1a** with 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) in acetic acid furnished a mixture of the 15-keto and 17-keto derivatives in approximately 1 : 2 ratio (by NMR). In order to alter the regioselectivity of oxidation, **1a** was hydrogenated over a palladium/charcoal catalyst[12] to yield **6a** which contains a biphenyl aromatic ring system (Chart II). Oxidation of **6a** with DDQ in acetic acid takes place regioselectiviely in the 17-position in accord with theoretical prediction [13] to furnish the 17-keto derivative **7a**. No significant concurrent dehydrogenation or oxidation appears to take place in the 6,7-bond under these conditions. Finally, dehydrogenation of **7a** over a Pd/charcoal catalyst provides pure **2a** in good overall yield. The assignment of **2a** as the 17-keto isomer is supported both by

Chart II



its melting point (mp 201-202°C, lit[14] 203-204°C) and by its 500 MHz NMR spectrum in comparison with the spectra of **1a** and the 15-keto isomer. Most notably, the H_7 bay region aromatic proton of **2a** is shifted slightly upfield from that of **1a**, and appears at δ 7.83 ppm, whereas H_7 of the 15-keto derivative is found at considerably lower field (δ 9.16 ppm) due to strong deshielding by the carbonyl function.

Syntheses of the 11-methyl-substituted analogs of **1a** and **2a** were accomplished by appropriate modification of the procedures outlined above. In the oxidation step with DDQ/HOAc no significant competitive oxidation on the methyl group was detected.



8 a: R = H; b: R = CH_3

There is now substantial evidence that metabolism of the cyclopenta[a]phenanthrenes affords diol epoxide metabolites, such as **8**,[4,15,16] that are the active forms that bind covalently to DNA in mammalian cells leading ultimately to tumor induction. However, the synthesis of these active carcinogenic metabolites has not yet been achieved. In principle, the general synthetic method in Charts I and II is also applicable to the synthesis of the phenolic derivatives required as starting compounds for the synthesis of the diol epoxide metabolites.[17] In order to demonstrate its feasibility for this purpose, the synthesis of 16,17-dihydro-3-methoxy-15H-cyclopenta[a]phenanthrene (**1c**) and its 17-keto derivative (**2c**) were carried out. 2-[1-(6-Methoxynaphthyl)]ethyl iodide (**3c**) required as the starting compound for this preparation, was synthesized from reaction of lithioethyl acetate[18] with 6-methoxy-1-tetralone followed by acid-catalyzed dehydration of the adduct and dehydrogenation to yield ethyl 1-(6-methoxynaphthyl) acetate. Reduction of this ester with $LiAlH_4$ provided the corresponding alcohol which on treatment with P_2I_4 yielded **3c**. Compound **3c** was utilized to synthesize **1c** in good overall yield via the sequence in Charts I and II.

Since methods for the conversion of the β-methoxy derivatives of polycyclic aromatic hydrocarbons to the corresponding diol epoxides have previously been developed[17], these biologically important molecules are now potentially accessible via the general synthetic approach described herein. Investigations directed towards the synthesis of the active diol epoxide metabolites of the cyclopenta[a]phenanthrenes **8a,b** are currently in progress and will be reported in due course.

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