Synthesis of a Bay-region Trifluoromethyl Analogue of a Potent Polycyclic Aromatic Carcinogen

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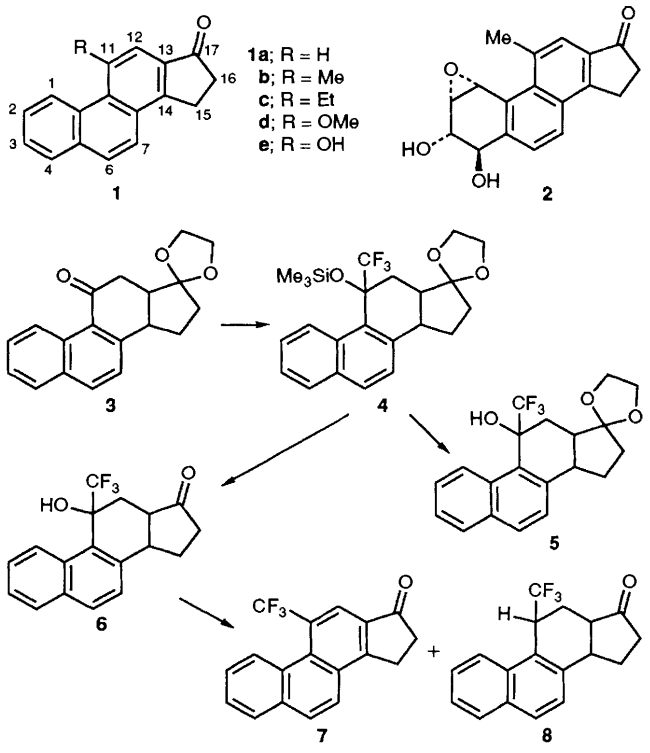
15,16-Dihydro-11-trifluoromethylcyclopenta[*a*]phenanthren-17-one **7**, an electronegative analogue of the strongly carcinogenic 11-methyl-17-ketone, is synthesised in three steps from 17,17-ethylenedioxy-11,12,13,14,15,16-hexahydrocyclopenta[*a*]phenanthren-11-one **3**.

It has long been known that substitution of a bay-region methyl group into the non-terminal benzo ring endows or enhances carcinogenicity in a variety of polycyclic aromatic compounds. Thus, benz[*a*]anthracene is only weakly active, whereas 7-methylbenz[*a*]anthracene is carcinogenic and 7,12-dimethylbenz[*a*]anthracene (DMBA) is a potent carcinogen.[1]

Cyclopenta[*a*]phenanthrenes are of interest because hydrocarbons of this series occur naturally in petroleum[2] and mineral oils,[3] in river and lake deposits,[4] and in overheated edible oils.[5] In all these sources they probably arise from dehydrogenation and side-chain cleavage of plant sterols. Compounds of the 17-ketone series such as **1a** are not only fully aromatic analogues of 17-ketosteroids, but also share structural similarities with the classical polycyclic aromatic hydrocarbons. As with the latter, introduction of a bay-region methyl group at C-11 in the ketone **1a**, itself inactive, produces the strong carcinogen **1b**.[6] This compound is similar in tumourgenicity on mouse skin to benzo[*a*]pyrene,[7] and like the latter it is activated metabolically to its 3,4-dihydro-3,4-*trans*-dihydroxy-1,2-*anti*-epoxide **2**[8] a compound recently synthesised by Harvey and coworkers. Carcinogenicity, although of a lower order, is exhibited also by the 11-ethyl **1c**[9] and 11-methoxy **1d** derivatives, and the 11-phenol **1e**.[10] All these are electron-releasing groups. In attempting to understand the reason for bay-region methyl enhancement of carcinogenicity in polycyclic aromatic compounds, it was of interest to substitute an electronegative group at C-11 in the parent ketone **1a** in order to study its effect on biological activity. The trifluoromethyl group was selected because it is only slightly larger in size than the methyl group and it would be anticipated that the shape[11] of molecules containing these groups would be similar. It is known that groups at C-11 larger than ethyl abolish carcinogenicity in this series.[9]

The oxoketal **3**[6] has been employed on several occasions to introduce substituents at C-11 in the parent ketone **1a**. Here, **3** was found to react smoothly with trifluoromethyltrimethylsilane[12] at ambient temperature in tetrahydrofuran (THF) in the presence of a catalytic amount of tetrabutylammonium fluoride to give the 11-trifluoro-11-trimethylsiloxy derivative **4** in 66% yield. Elimination of the 11-oxygen atom from this molecule, however, required drastic conditions. Treatment with boron trifluoride–ether in dichloromethane, a method recently recommended[13] for the dehydration of siloxy tertiary alcohols, resulted merely in removal of the silyl group to yield the alcohol **5**. This compound was more conventionally secured by the use of tetrabutylammonium fluoride in damp THF. **5** was stable to the action of phosphoryl chloride in pyridine at room temperature, but at the boil it was slowly converted into several products including a small amount of the expected 11,12-ene, as revealed by TLC and UV spectral examination. On being heated under reflux with concentrated hydrochloric acid in dioxane the trimethylsilyloxy ketal **4** gave the hydroxy ketone **6** with no indication of dehydration. This was finally effected by treatment of the latter with thionyl chloride in pyridine at ambient temperature; use of this technique at or below 0 °C has been reported for the dehydration of hindered tertiary alcohols,[14] and it was



expected that a trigonal carbon atom at C-17 would assist aromatisation. As anticipated, the product was not the 11,12-ene, but a mixture of approximately equal amounts of the desired 11-trifluoromethyl-17-ketone **7** and its 11,12,13,14-tetrahydro derivative **8**, obtained together in about 25% yield. Similar disproportionation occurred during the acid-catalysed dehydration of the methyl tertiary alcohol coresponding to **5**, but in this case the 11-methyl-17-ketone **1b** was obtained in virtually quantitative yield by addition of a mild oxidising agent such as nitrobenzene to the acid reaction mixture.[6] Here, addition of nitrobenzene to the pyridine–thionyl chloride mixture appeared to have little effect on either the yield or the ratio of the two compounds formed; the reason for the low yield of these two compounds is not clear at present. They were readily separated by column chromatography on flash silica by elution with dichloromethane. Dehydrogenation of the tetrahydro compound **8** by heating it in triglyme with 5% palladium on charcoal at 210 °C yielded a further quantity of the phenanthrene **7**.

15,16-Dihydro-11-trifluoromethylcyclopenta[*a*]phenanthren-17-one **7** formed pale-yellow needles (from methanol): m.p. 171–172 °C; IR ν_{max}/cm^{-1} (Nujol) 1713 (C=O); the UV spectrum of **7** [λ_{max}/nm (log ε) 229 (4.81), 272.5 (5.43), 300 sh, 338.5 (3.76), 355 (3.87), 373 (3.86)] is similar to that of other 17-ketones of this series.[15] In its 300 MHz ^{1}H NMR spectrum ($CDCl_3$, Me_4Si) δ 8.84 (1H, dd, 1-H), 8.43 (1H, s, 12-H), 7.97 (3H, m, aromatic), 7.71 (2H, m, aromatic), 3.57 (2H, m, 15-H), 2.94 (2H, m, 16-H) 12-H resonates 0.7 ppm downfield compared with the same proton in the 11-methyl-17-ketone **1b** whereas 1-H remains at approximately the same position. However, in the ^{13}C NMR spectrum of **7** both C-12 and C-1 show similar fluorine couplings, δ ($CDCl_3$ used as solvent and secondary reference) 121.9 ($J_{F\text{-}^{13}C}$ 7.55 Hz) and 128.7 ($J_{F\text{-}^{13}C}$ 8.2 Hz), respectively, indicating that the distances between these carbons and the fluorine atoms are similar. From a computer model of this compound, based on that of its 11-methyl analogue (itself derived from the experimental X-ray coordinates[11]) with the same C(1)–C(10)–C(9)–C(11) torsion angle of 13.5°, these distances are 2.71 and 2.64 Å, in agreement with this suggestion. The biological properties of this trifluoromethyl analogue will be reported elsewhere at a later date.

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