A Kinetic Investigation of the Hydroxide-catalysed Detritiation of Various [16-^{3}H]-15,16-Dihydrocyclopenta[*a*]phenanthren-17-ones and Related Compounds

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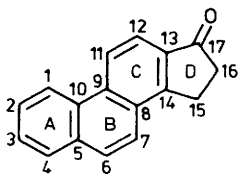
The hydroxide-catalysed detritiation rate constants from the C-16 position of a series of substituted [16-^{3}H]-15,16-dihydrocyclopenta[*a*]phenanthren-17-ones have been measured in a 90:10 (v/v) water–dioxane mixture at 25 °C. The results show that methyl group substitution brings with it, in addition to the customary deactivating effect, a marked acceleration in rate, which probably has its origin in steric strain considerations. Similar studies involving the analogous position in a number of related ketones (benz[*e*]indanone, indanone, and cyclopentanone) show that the rates are not simply a function of the number of additional benzene rings but depend on their position relative to the cyclopentanone system.

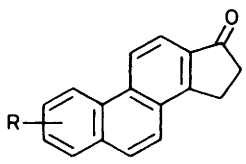
The 15,16-dihydrocyclopenta[*a*]phenanthren-17-ones (**1a**), which are structurally related to both polycyclic aromatic hydrocarbon carcinogens and natural steroids, provide an attractive model for investigating the mechanisms of carcinogenesis, as considerable knowledge of their chemistry, metabolism, and biological properties have been obtained in recent years.[1] Thus, methyl substitution in the parent compound, which itself is not carcinogenic, leads to a wide range of activity. The 11-methyl isomer is strongly carcinogenic, being similar in potency to benzo[*a*]pyrene,[2] whilst the 7-methyl isomer is a weak carcinogen and the 2-, 3-, 4-, 6-, and 12-methyl isomers are inactive.[1] The 11-methoxy isomer is moderately active but other methoxy isomers lack activity.

Many attempts[3,4] have been made at correlating carcinogenicity with either initial state features or with reactivity of the substrates towards some common reactant; theoretical calculations have also been made with the same objectives in mind. As far as the cyclopenta[*a*]phenanthrenones involved in the present investigation are concerned *X*-ray studies[5] show that deviations from planarity are most pronounced for the 11-methyl compound (**1g**), the deformation of the benzo rings being as high as 12.5°. Two other carcinogens (**1f**) (7-Me) and (**1o**) (1,11-methano) are distinguished by high angle strain.

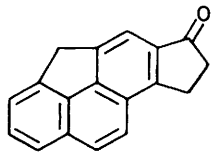
The presence of a keto group at C-17 in the dihydrocyclopenta[*a*]phenanthrenones points to the possibility of studying base-catalysed hydrogen-isotope exchange at the adjacent C-16 position and witnessing the effect substituents, particularly methyl groups, have on the rate. Furthermore, as compounds (**2**)—(**4**) are either available or easily synthesized the effect of gradually removing the benzene rings on the rates can be ascertained. It was for these reasons that the present investigation was undertaken.



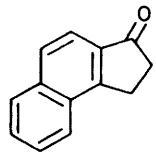
(**1a**)



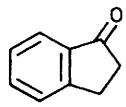
(**1**)**b**; R = 1-Me
c; R = 3-Me
d; R = 4-Me
e; R = 6-Me
f; R = 7-Me
g; R = 11-Me
h; R = 12-Me
i; R = 11-Me, 12-Me
j; R = 7-Me, 11-Me
k; R = 11-OH
l; R = 11-OMe
m; R = 7-Me, 11-OMe
n; R = 11-Et



(**1o**)



(**2**)



(**3**)

(**4**)

Experimental

Materials.—Most of the compounds were obtained in a pure state as a result of previously reported syntheses, *e.g.*, (**1a**, **g**, **h**, **i**),[6] (**1c**, **d**, **e**),[7] (**1b**, **j**, **o**),[8] (**1f**).[9] Both cyclopentanone and indanone were commercially available and purified prior to use whilst the benz[*e*]indanone was synthesized in essentially the same manner as described by Danneburg and Rahmen.[10]

The dihydrocyclopenta[*a*]phenanthren-17-ones, which were available in small quantities, were tritiated by dissolving 5—10 mg in dioxane (1 ml) before adding a pellet of sodium hydroxide or a drop of concentrated hydrochloric acid followed by tritiated water (5 μl; 50 Ci ml^{-1}) and leaving at room temperature for 2—3 days. The labelled product was then washed with water prior to extracting into diethyl ether; drying (anhydrous sodium sulphate), followed by freeze-drying off of the solvent gave the required material which was then dissolved in 50 μl of deuteriated solvent (usually $CDCl_3$), the total

radioactivity determined and if sufficient (> 1 mCi) the sample was subjected to ^3H n.m.r. analysis. In some cases the base-catalysed procedure led to some by-product formation. For these compounds, (**1a**, **g**, **h**, and **i**), further purification was effected by thin-layer chromatography. In general the acid-catalysed procedure caused less by-product formation.

Both indanone and benz[*e*]indanone were also tritiated by the base-catalysed procedure whilst the method adopted for cyclopentanone was similar to that used for its deuteriation.[11,12] The compound (200 μl), diethyl ether (0.5 ml), tritiated water (10 μl; 50 Ci ml^{-1}), potassium carbonate (8 mg), and sodium chloride (40 mg) were placed in a sealed tube and the contents kept at room temperature for two weeks. Addition of water followed by extraction with diethyl ether, drying (anhydrous sodium sulphate) and careful removal of solvent by slow passage of a stream of nitrogen over the surface of the solution gave the required product.

Kinetics.—Because of the insolubility of the dihydrocyclopenta[*a*]phenanthren-17-ones in water the hydroxide-catalysed detritiations were carried out in a 90:10 (v/v) water–dioxane mixture; the same system was employed for all the other ketones. The customary procedure was to add a trace amount of the labelled substrate to the reaction medium (100 ml) in a thermostat and withdraw samples (5 ml) at fixed time intervals and inject into tubes containing scintillator (10 ml; 3.4 g l^{-1} 2,5-diphenyloxazole in toluene) and water (10 ml). The mixture was shaken, the toluene layer was separated and dried (Na_2SO_4) and the tritium content of a portion (5 ml) determined. The first-order detritiation rate constants (k^T) were calculated from the slopes ($-k^T/2.303$) of the plots of log (counts min^{-1}) against time and converted into second-order rate constants ($k^T_{OH^-}$) by dividing by the hydroxide ion concentration. The uncertainty in the values of $k^T_{OH^-}$ for the simple ketones (**2**)—(**4**) (Table) amounts to 2—4%, comparable to those obtained in other similar studies. For some of the dihydrocyclopenta[*a*]phenanthren-17-ones the uncertainty is a good deal higher (± 10%) and this could be associated with the difficulties encountered in the base-catalysed tritiations.

Results and Discussion

Nearly all the ketones labelled contained sufficient radioactivity for ^3H n.m.r. analysis to be performed. The ^1H-decoupled spectra for the purified ketones gave one sharp signal (δ 2.7—2.86, $CDCl_3$ solvent). From the kinetics good linear first-order plots were obtained. Clearly the *exo*- and *endo*-forms of the C-16 hydrogens are equivalent and equally reactive.

The change from a purely aqueous medium to a 90:10 (v/v) water–dioxane mixture is unlikely to have a large effect on the rate and this is confirmed by the finding that $k^T_{OH^-}$ for acetophenone (5.81×10^{-3} M^{-1} s^{-1}) differs by less than 10% from the value in water[13] (5.50×10^{-3} M^{-1} s^{-1}). The results in the Table show that the rate constant for the unsubstituted dihydrocyclopenta[*a*]phenanthren-17-one has virtually the same value as for the 1-methyl ketone and is some 20—23% higher than for the 3- and 4-methyl isomers. These findings are consistent with the weakly electron-donating properties of the methyl group and the relatively large distance which separates ring A from the keto group. The effect is more pronounced for the 6-methyl isomer and, for the singly substituted ketones, is at its maximum for the 12-methyl compound, where the rate is nearly a third that of the parent ketone (**1a**). Whilst these findings are in line with theory the same cannot be said for the results for the 7-methyl isomer, where a considerable rate enhancement is observed. Other 7-methyl-substituted compounds (**1j** and **1m**) also show rates faster than for the parent ketone (**1a**).

Table. Hydroxide-catalysed detritiation rate constants ($k^T_{OH^-}$) at 298.2 K for various [16-^3H]-15,16-dihydrocyclopenta[*a*]phenanthren-17-ones and related compounds.

Compound	$10^2 k^T_{OH^-}$/ M^{-1} s^{-1}	Compound	$10^2 k^T_{OH^-}$/ M^{-1} s^{-1}
(**1a**)	1.83 ± 0.14	(**2**)	1.12 ± 0.05
(**1b**)	1.85 ± 0.05	(**3**)	2.37 ± 0.09
(**1c**)	1.42 ± 0.02	(**4**)	0.65 ± 0.02
(**1d**)	1.47 ± 0.19		
(**1e**)	1.15 ± 0.14		
(**1f**)	3.17 ± 0.08		
(**1g**)	1.47 ± 0.06		
(**1h**)	0.67 ± 0.07		
(**1i**)	0.30 ± 0.05		
(**1j**)	2.45 ± 0.19		
(**1k**)	0.23 ± 0.02		
(**1l**)	2.06 ± 0.06		
(**1m**)	2.50 ± 0.17		
(**1n**)	1.58 ± 0.03		
(**1o**)	0.87 ± 0.07		

In a fully aromatic structure delocalisation of charge through resonance is usually an important factor in stabilising carbanion formation and hence increasing carbon acidity. In the partly aromatic structures studied here it is this deviation from planarity, which as *X*-ray studies[5] show, result in steric strain, which is probably the cause of the anomalous reactivity pattern observed. It is interesting to note that difficulties experienced in synthesizing the 7-methyl compound by the standard methods used in obtaining other members of the series have been attributed to the same cause. Although the contribution of ring strain to reactivity is difficult to quantify there are now many examples[14,15] where considerable rate accelerations can be ascribed to this factor. In the present study it would have to account, at least partly, for a rate acceleration [*e.g.*, (**1f**), 7-Me], retardation (**1o**), and effectively no change (**1g**).

The results for the 11-hydroxy ketone (**1k**) show that the detritiation rate is the slowest for all the compounds investigated and this finding is consistent with the fact that under the conditions of high pH used in the kinetics the group is ionised and the compound reacts as the anion.

The influence of the benzene rings on the detritiation rates can best be seen by initially comparing the results for cyclopentanone (**4**) and indanone (**3**); a four-fold acceleration in rate can probably be ascribed to the extra rigidity provided by the benzene ring. It is interesting to speculate on whether the addition, in a linear manner, of a second benzene ring would have led to a continuation of this trend. However, synthetic considerations dictated that benz[*e*]indanone was prepared and here we see a two-fold reduction in rate, probably because the additional ring causes a small deviation from planarity. Interestingly the addition of a further benzene ring to give the dihydrocyclopenta[*a*]phenanthren-17-one brings with it a 60% increase in reactivity. One can therefore conclude that the effect of additional benzene rings is not simply additive but depends on factors such as deviations from planarity, which in themselves are a cause of ring strain.

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