product, isolated as usual, was chromatographed over silica gel to yield 4,5-dimethyl-9,10-phenanthrenequinone, mp 161–163 °C, which was not depressed on mixing with an authentic sample,[23] mp 163–164 °C.

**9-Bromo-2,4,5,7-tetramethylphenanthrene* (7).** By a procedure similar to that described above **2** was converted in 38% yield into **7**: mp 110.5–112.0 °C; mass spectrum,[18] peaks at m/e 312 and 314 of about equal intensity; NMR ($CDCl_3$, $Me_4Si$) $\delta$ 2.55 (br s, 12, $ArCH_3$), 7.46 (m, 3 $H_{pos-3,6,8}$), 7.80 (s, 1, $H_{pos-10}$), 7.95 (br s, 1 $H_{pos-1}$). Oxidation to 2,4,5,7-tetramethyl-9,10-phenanthrenequinone was readily effected as above. The quinone was converted in high yield into the quinoxaline derivative,[23] which was identified by its melting point and mixture melting point with quinoxaline prepared from authentic **2**, mp 230.0–230.5 °C, by reaction with *o*-phenylenediamine.

**9-Bromo-3,4,5,6-tetramethylphenanthrene* (8).** As above, **3** was converted in 25% yield into **8**: mp 69.5–73.0 °C; mass spectral peaks at *m/e* 312 and 314 of about equal intensity;[18] NMR ($CDCl_3$, $Me_4Si$) $\delta$ 2.44 (m, 12, $ArCH_3$), 7.37–7.64 (m, 3, ArH), 7.77 (s, 1, $H_{pos-10}$), 8.07 (perturbed d, $J$ = 8 Hz, 1, $H_{pos-1}$). Oxidation afforded 3,4,5,6-tetramethyl-9,10-phenanthrenequinone, identified as its quinoxaline derivative,[23] mp and mmp 178.5–180.0 °C.

**9-Bromo-2,7-dimethylphenanthrene* (9) and 9-Bromo-3,6-dimethylphenanthrene* (10).** These compounds were prepared by adding a slight excess of bromine to solutions of **4** and **5** in $CCl_4$ at 0 °C. After 2 h at ambient temperature the solvent was removed by rotary evaporation and the remainder heated on a steam bath for 30 min. After dry column chromatography on silica gel (activity grade III) using hexane, there was obtained 65% yield of **9** [mp 100–101 °C (analytical sample 102.5–103.5 °C); mass spectrum, peaks at *m/e* 284 and 286 of about equal intensity; NMR ($CDCl_3$, $Me_4Si$) $\delta$ 2.50 (s, 3, $ArCH_3$), 2.57 (s, 3, $ArCH_3$), 7.37–7.50 (m, 3, $H_{pos-2,6,8}$), 7.97 (s, 1, $H_{pos-10}$), 8.14 (br s, 1, $H_{pos-1}$), 8.44 and 8.57 (both br s, 2, $H_{pos-4,5}$)] and a 50% yield of **10** [mp 64–66 °C (analytical sample 66–67 °C); mass spectrum, peaks at *m/e* 284 and 286 of about equal intensity; NMR ($CDCl_3$, $Me_4Si$) $\delta$ 2.58 (br s, 6, $ArCH_3$), 7.27–7.74 (m, 3, $H_{pos-2,7,8}$), 7.97 (s, 1, $H_{pos-10}$), 8.25 (d, $J$ = 5 Hz, 1, $H_{pos-1}$), 8.44 (br s, 2, $H_{pos-4,5}$)].

**Registry No.** **1**, 3674-69-9; **2**, 7396-38-5; **3**, 7343-06-8; **4**, 1576-69-8; **5**, 1576-67-6; **6**, 71871-02-8; **7**, 71871-03-9; **8**, 71871-04-0; **9**, 71871-05-1; **10**, 71871-06-2; **13**, 3594-91-0; **14**, 7411-15-6; **15**, 7343-08-0; **16**, 2941-81-3; **17**, 71871-07-3; **18**, 71871-08-4; **19**, 71871-09-5; **20**, 71871-10-8; 6,6′-dimethyl-2,2′-diphenic acid, 71871-11-9; *o*-toluidine, 95-53-4; 2-methylisonitrosoacetanilide, 1132-03-2; 7-methylisatin, 1127-59-9; 2-amino-3-methylbenzoic acid, 4389-45-1; 4,4′-dimethyl-2,2′-diphenic acid, 2941-79-9; *p*-toluidine, 106-49-0; diethyl 6,6′-dimethyl-2,2′-diphenate, 71871-12-0; diethyl 5,5′,6,6′-tetramethyl-2,2′-diphenate, 71871-13-1; 5,5′,6,6′-tetramethyl-2,2′-diphenic acid, 7343-07-9; sodium amide, 7782-92-5; 4,4′-*trans*-dimethylstilbene, 18869-29-9; 4,5-dimethyl-9,10-phenanthrenequinone, 17825-37-5; 2,4,5,7-tetramethyl-9,10-phenanthrenequinone, 17825-38-6; 2,4,5,7-tetramethyl-9,10-phenanthrenequinone quinoxaline derivative, 17825-39-7; *o*-phenylenediamine, 95-54-5; 3,4,5,6-tetramethyl-9,10-phenanthrenequinone, 17825-40-0; 3,4,5,6-tetramethyl-9,10-phenanthrenequinone quinoxaline derivative, 17825-41-1.

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# Electrophilic Aromatic Substitution. 25.[1] Acid-Catalyzed Hydrogen Exchange of 9-Tritiated Polymethylphenanthrenes: Effect of Ring Distortion on Aromatic Reactivity and Substituent Effects[2]

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Rate coefficients have been measured for detritiation of the 9-position of some strained and unstrained polymethylphenanthrenes by anhydrous trifluoroacetic acid at 70 °C. These lead to partial rate factors (in parentheses) as follows: 2,7-dimethylphenanthrene (12 950), 3,6-dimethylphenanthrene (59 800), 3,4,5,6-tetramethylphenanthrene (356 000), 4,5-dimethylphenanthrene (38 300), 2,4,5,8-tetramethylphenanthrene (230 000). The reactivities of the former two (unstrained) compounds are in excellent agreement with those predicted from the effects of monomethyl substituents in phenanthrene. By contrast the reactivities of the latter two compounds are approximately threefold greater than predicted due to steric interaction of the 4- and 5-methyl substituents; these produce nonplanarity of the aromatic rings and hence increased reactivity through loss of ground-state resonance. The strained 3,4,5,6-tetramethylphenanthrene is by contrast *less* reactive than predicted, this being attributable to substantial reduction, through distortion, of the conjugative interaction between the 3- and 9-positions (which is normally much greater than the other substituent site interactions).

In this series of papers we have sought to determine, mainly through the use of an acid-catalyzed hydrogen-exchange reaction, quantitative reactivity data for aromatic hydrocarbons. Advantages of the reaction (among others) are freedom from steric hindrance and accuracy of the kinetic method. Recently we have determined[4] the effects of methyl substituents at each of the 1–8-positions upon the rate of exchange of tritium at the 9-position in trifluoroacetic acid at 70 °C. The data are shown in Figure 1 where the numbers indicate the activating effect of a methyl group at the appropriate position on the rate of tritium exchange at the 9-position. (Because 1,2-hydrogen shifts occur across the 9,10-bond of methylphenanthrenes during hydrogen exchange,[5] a significant error is introduced if the activating effect of a 6- and 8-methyl substituent in a symmetrically substituted polymethylphenanthrene is calculated from the raw data.[4] The corrected activating effects for these substituents are therefore given, in parentheses, in Figure 1. For the other substituents the errors are trivial so no correction need be applied.)

(1) Part 25. M. M. J. Le Guen, Y. El-din Shafig, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, in press.

(2) This work was supported by NATO.

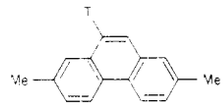
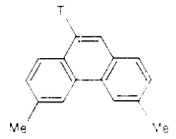
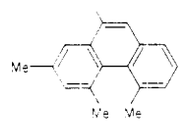
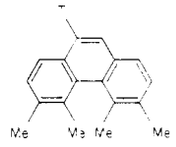
(3) Postdoctoral Research Associate.

(4) H. V. Ansell, P. J. Sheppard, C. F. Simpson, M. M. A. Stroud, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, in press.

(5) H. V. Ansell, P. J. Sheppard, C. F. Simpson, M. M. A. Stroud, and R. Taylor, *J. Chem. Soc., Chem. Commun.*, 587 (1978).

0022-3263/79/1944-4946$01.00/0 

Table I. Rate Coefficients and Partial Rate Factors for Protiodetritiation of Ar-9-*t* Anhydrous Trifluoroacetic Acid at 70 °C

| Ar-9-*t* | no. | $10^7 k_{obsd}$, $s^{-1}$ | $10^7 k_{calcd}$, $s^{-1}$ | $k_{obsd}/k_{calcd}$ | *f* | $\sigma^+$ [a] |
|---|---|---|---|---|---|---|
|  | 1 | 1 230 | 1 300 | 0.95 | 12 950 | −0.47 |
|  | 2 | 5 680 | 5 830 | 0.97 | 59 800 | −0.54 |
|  | 3 | 3 640 | 1 080 | 3.37 | 38 300 | −0.52 |
|  | 4 | 21 850 | 9 060 | 2.41 | 230 000 | −0.61 |
|  | 5 | 33 850 | 40 750 | 0.83 | 356 000 | −0.63 |

[a] Defined by $\log f/-8.8$ where $f = k(\text{Ar-}x\text{-}t)/k(\text{benzene-}t)$.

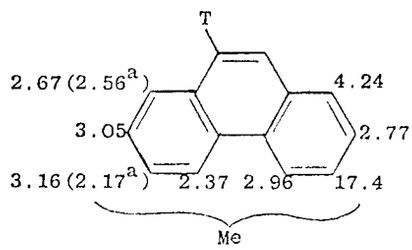



**Figure 1.** Activating effects of methyl substituents on exchange at the 9-position of phenanthrene. See the text about the numbers marked with a superscript a.

The availability of these data has meant that the effect of distortion of the phenanthrene ring system (which occurs in certain polymethylphenanthrenes) can be measured quantitatively in terms of electrophilic aromatic reactivity. Previously, the effects of multiple methyl substituents have been measured in both benzene[6] and naphthalene,[7] and the agreement between observed and calculated rates is excellent over a very wide reactivity range ($10^8$). Thus in phenanthrene, similar agreement should obtain, and any deviations which occur may therefore be reasonably attributed to the incursion of the effects of steric strain. Accordingly, a research program was undertaken in cooperation with Professor M. S. Newman[15] in order to investigate these ring-strain effects.

## Results and Discussion

Rate coefficients for exchange of 9-tritiated polymethylphenanthrenes (**1**–**5**) were measured in anhydrous trifluoroacetic acid at 70 °C and could be duplicated to better than ±2%. These are given in Table I along with the rate coefficients predicted from the monomethyl substituent effects (Figure 1), the partial rate factors (the rate coefficient for detritiation of benzene under the same conditions is $0.095 \times 10^{-7}$ $s^{-1}$[19]), and $\sigma^+$ values ($\rho$ is −8.8).[10] The main features of the results are as follows.

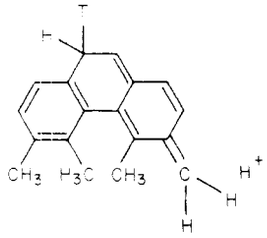
(i) For planar 2,7-dimethylphenanthrene, and planar 3,6-dimethylphenanthrene, agreement between observed and calculated rates of exchange is excellent, the observed reactivity being slightly less than predicted in each case. Each additional methyl substituent produces a more reactive system, the transition state for reaction of which will be nearer to the ground state so that the effects of subsequent substituents will be smaller; i.e., the reactivity–selectivity effect operates.[11] It may be noted that the good agreement between the observed rate coefficient for 3,6-dimethylphenanthrene and that calculated by correcting for the 1,2-hydrogen shift across the 9,10-bond[5] further confirms the existence of this shift. (Without this correction the predicted rate coefficient would be $8600 \times 10^{-7}$ $s^{-1}$, significantly higher than that obtained.)

(ii) For the nonplanar 4,5-dimethylphenanthrene there is a most marked divergence between observed and calculated rate coefficients, the former being over threefold greater. This can be attributed to the loss of conjugation and hence ground-state stability of the molecule arising from the twisting of the phenanthrene framework caused by interaction of the adjacent methyl groups. Interestingly, the reactivity increase is of a similar magnitude to that observed in tetra-,[11] penta-,[1] and hexahelicenes,[12] which are ca. 3-, 7-, and 11-fold more reactive, respectively, than they are calculated to be. These data, taken along with the results for 10-annulenes[13] constitute, as far as we are

(6) K. E. Richards, A. L. Wilkinson, and G. J. Wright, *Aust. J. Chem.*, **25**, 2369 (1972); R. Taylor, *Aromat. Heteroaromat. Chem.*, **2**, 226 (1974).
(7) H. V. Ansell and R. Taylor, *Tetrahedron Lett.*, 4915 (1971).
(8) H. V. Ansell and R. Taylor, *J. Chem. Soc., Chem. Commun.*, 952 (1973).
(9) R. Baker, C. Eaborn, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 97 (1972).
(10) For a discussion of the principles involved, see R. Taylor, *Aromat. Heteroaromat. Chem.*, **4**, 247 (1976); **1**, 188 (1973).
(11) M. M. J. Le Guen and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1274 (1974).
(12) Y. El-din Shafig and R. Taylor, unpublished work.

aware, the only reactivity data which demonstrate the enhanced reactivity of an aromatic ring arising from loss of conjugation in the ground state.

(iii) Although the present results indicate a reactivity increase due to loss of planarity of just over threefold, the true value may be rather greater, because the methyl substituent effects should be diminished by the loss of conjugation. This is strongly suggested by the results for **4** which should be the product of the results for **1** and **3**. That it is not indicates that the 2- and 7-methyl substituent effects observed in planar **1** become diminished in nonplanar **4**. The effect is especially noticeable in **5** which possesses a 3-methyl substituent, this latter being by far the most strongly activating of all the methyl substituents because of the strong 3,9-conjugative interaction (**6**). In



**6**

addition, formation of the hyperconjugative structure **6** will be inhibited by the presence of the adjacent (and buttressed) methyl group. Consequently, compound **5**, although severely distorted, is actually less reactive than predicted from the additive effects of the normal methyl substituent effects.

This study shows, therefore, that noncoplanarity produces both increased reactivity and reduced substituent effects. We plan to examine the significance of these factors in determining the carcinogenic behavior of some aromatic hydrocarbons.

## Experimental Section

The appropriate bromo aromatics in ether were treated with an excess of 1.5 M *n*-BuLi in hexane, warmed for a few minutes, and then treated with tritiated water of sufficient activity to produce products of ca. 0.5 mCi/g. Normal workup followed by column chromatography (elution with petroleum ether) gave products which melted to within 1 °C of the literature values.

Kinetic studies were carried out in the normal way.[14] It was discovered that addition of trifluoroacetic acid to the aromatic deposited in the ampules produced an instantaneous reaction during mixing, and this resulted in an initial substantial loss of activity. This is a surface-catalyzed reaction which evidently ceases once removal of the aromatic from the glass surface is complete, and this is being investigated more fully. The effect can be minimized by using relatively larger ratios of aromatic to acid per ampule and freshly purified acid; when this is done, normal first-order kinetics are obtained.

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**Registry No.** **1**, 71886-33-4; **1**, 9-bromo derivative, 71871-05-1; **2**, 71886-34-5; **2**, 9-bromo derivative, 71871-06-2; **3**, 71886-35-6; **3**, 9-bromo derivative, 71871-02-8; **4**, 71886-36-7; **4**, 9-bromo derivative, 71871-03-9; **5**, 71886-37-8; **5**, 9-bromo derivative, 71871-04-0.

(13) R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 1287 (1975).

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(15) M. S. Newman and Kenneth C. Lilje, *J. Org. Chem.*, preceding paper in this issue.

# Synthesis of Biologically Active Metabolites of 7-Methylbenz[*a*]anthracene

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Syntheses are described of the trans 3,4-dihydro diol (**1a**) and the corresponding anti diol epoxide (**2**) of 7-methylbenz[*a*]anthracene, implicated as proximate and ultimate carcinogenic metabolites, respectively, of this potent precarcinogen. Additional syntheses are reported of the related trans 1,2-dihydro diol (**3a**), the corresponding anti and syn diol epoxides, and 2- and 3-hydroxy-7-methylbenz[*a*]anthracene, additional potential metabolites of this polycyclic hydrocarbon.

7-Methylbenz[*a*]anthracene (MBA) is one of the most potent known carcinogenic polycyclic hydrocarbons.[1,2] Metabolic studies[3-5] have implicated the trans 3,4-dihydro diol (**1a**) as a proximate[6] carcinogenic metabolite and *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (**2**) as the principal ultimate[6] carcinogenic metabolite of this hydrocarbon. Despite the biological significance of these compounds, syntheses of **1a** and **2** have not yet been achieved.[7] The synthetic approaches devised earlier for the analogous dihydro diol and diol epoxide metabolites of other polycyclic hydro-

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(4) Vigny, P.; Duquesne, M.; Coulomb, H.; LaCombe, C.; Tierney, B.; Grover, P. L.; Sims. P. *FEBS Lett.* **1977**, *75*, 9.

(5) Chouroulinkov, I.; Gentil, A.; Tierney, B.; Grover, P.; Sims, P. *Cancer Lett.* **1977**, *3*, 247.

(6) A *proximate carcinogen* is defined as a metabolically activated intermediate precursor of the *ultimate carcinogen* which is the active form which interacts with the critical receptor, generally believed to be DNA, leading to induction of cancer: Miller, J. *Cancer Res.* **1970**, *30*, 559.

(7) Oxidation of MBA by ascorbic acid–ferrous sulfate–EDTA afforded various dihydro diols and other oxidized products from which **1** was isolated by LC in <0.2% yield: Tierney, B.; Abercrombie, B.; Walsh, C.; Hewer, A.; Grover, P. L.; Sims, P. *Chem.-Biol. Interact.* **1978**, *21*, 289.

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