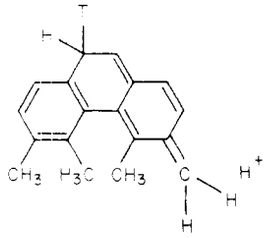
aware, the only reactivity data which demonstrate the enhanced reactivity of an aromatic ring arising from loss of conjugation in the ground state.

(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.

Acknowledgment. We thank NATO for financial support of this work.

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).

(14) H. V. Ansell, M. M. Hirschler, and R. Taylor, *J. Chem. Soc., Perkin Trans. 2*, 353 (1977); J. M. Blatchly and R. Taylor, *J. Chem. Soc.*, 4641 (1964).

(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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Received July 17, 1979

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-

(1) "International Agency for Research on Cancer: Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic and Heterocyclic Compounds"; World Health Organization: Geneva, Switzerland, 1973; Vol. 3.

(2) Huggins, C. B.; Pataki, J.; Harvey, R. G. *Proc. Natl. Acad. Sci. U.S.A.* **1967**, *58*, 2253.

(3) Tierney, B.; Hewer, A.; Walsh, C.; Grover, P. L.; Sims, P. *Chem.-Biol. Interact.* **1977**, *18*, 179.

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

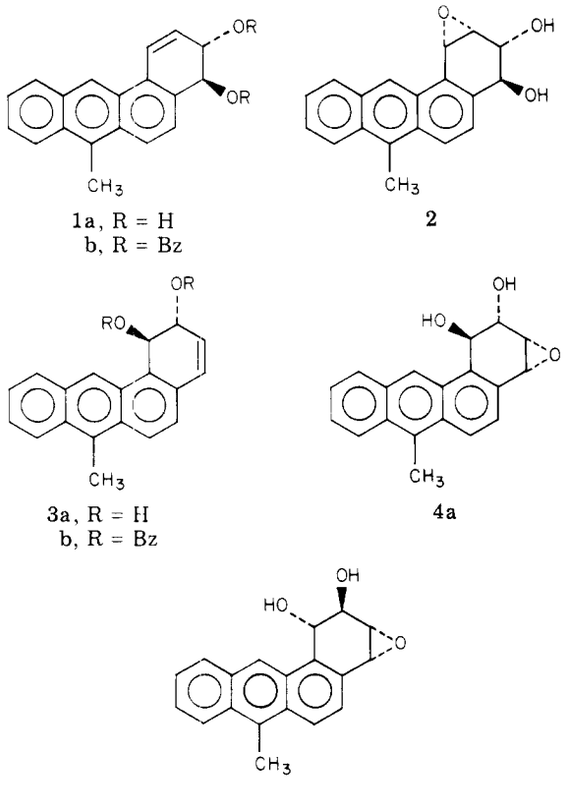
(5) Chouroulinkov, I.; Gentil, A.; Tierney, B.; Grover, P.; Sims, P. *Cancer Lett.* **1977**, *3*, 247.

(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.

0022-3263/79/1944-4948$01.00/0

Chart I



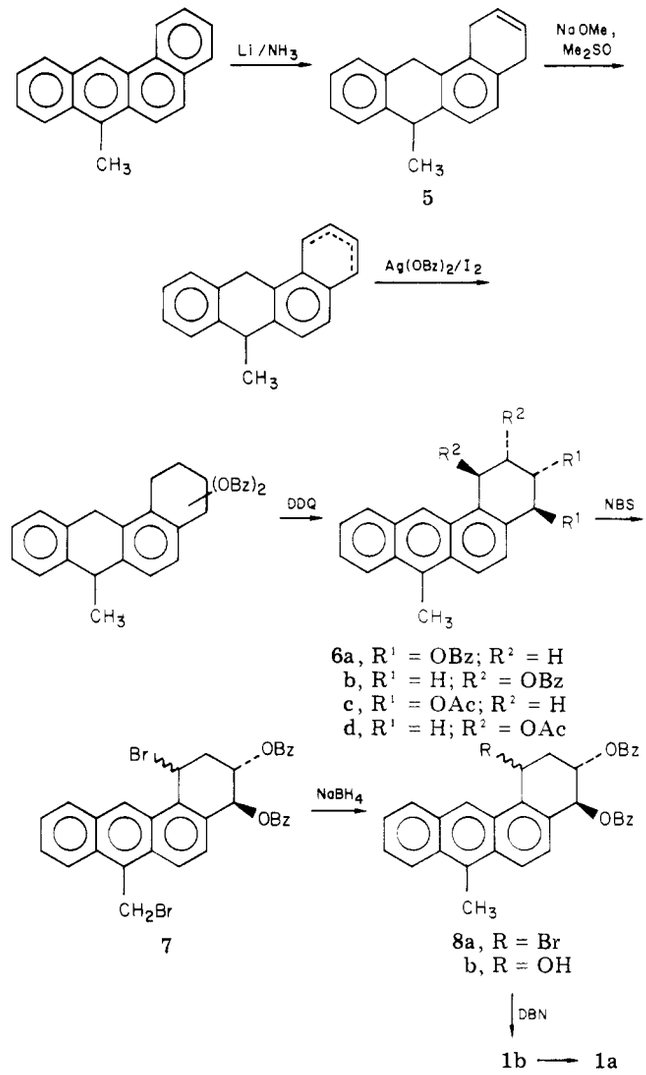
carbons[8] are not directly applicable as a consequence of the likelihood of seriously competitive side reactions in the reactive meso region or on the methyl group.

We now report convenient syntheses of **1a** and **2**, the isomeric trans 1,2-dihydro diol (**3a**), and the corresponding anti diol epoxide derivative (**4**), as well as 2- and 3-hydroxy-7-methylbenz[a]anthracene potential phenolic metabolites of MBA.[9]

Results

Two synthetic approaches to **1a** and **2** were developed. Method I outlined in Scheme I is a modification of the reaction sequence described earlier for the synthesis of the corresponding derivatives of benz[a]anthracene.[10] The MBA required as starting material was conveniently synthesized from benz[a]anthracene through bromination, reaction with phenyllithium to generate 7-lithiobenz[a]anthracene, and methylation with methyl iodide. Stepwise reduction of MBA with lithium in liquid ammonia[11,12] afforded 1,4,7,12-tetrahydro-7-methylbenz[a]anthracene (**5**) in excellent yield. Isomerization of **5** took place smoothly on treatment with $NaOCH_3$ in Me_2SO in the absence of air to furnish the conjugated olefins 1,2,7,12- and 3,4,7,12-tetrahydro-7-methylbenz[a]anthracene in the ratio of 55:45 essentially quantitatively. Prévost reaction

Scheme I



of this mixture with 1 equiv of silver benzoate and iodine gave the corresponding trans diol dibenzoates in 79% yield; reactions employing more than stoichiometric ratios of the reagent afforded secondary products of side-chain iodination. Dehydrogenation with DDQ in refluxing benzene provided the related trans diol dibenzoates of 1,2,3,4-tetrahydro-7-methylbenz[a]anthracene (**6a,b**) in the ratio of 3:2 in 66% yield. The latter were readily separated by fractional crystallization from ether. Introduction of an olefinic bond into the 1,2-positions of the major isomer **6a** by the usual bromination–dehydrobromination procedure[8,13] was complicated by the greater facility of bromination by NBS on the reactive methyl group. This difficulty was surmounted through conducting bromination with 2 equiv of NBS to provide a mixture of the epimeric dibromo derivatives **7**, followed by selective reduction of the 7-bromomethyl group. The latter was accomplished efficiently with $NaBH_4$ in diglyme.[14] Reduction of **7** with $NaBH_4$ in Me_2SO[15] resulted in concurrent formation of *trans*-3,4-bis(benzoyloxy)-1-hydroxy-1,2,3,4-tetrahydro-7-methylbenz[a]anthracene (**8b**). The monobromo derivative **8a** underwent dehydrobromination with DBN to

(8) (a) Review: Harvey, R. G.; Fu, P. P. In "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism"; Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 1, p 133. (b) For more recent references cf.: Harvey, R. G.; Lee, H. M.; Shyamasund .. N. *J. Org. Chem.* **1979**, *44*, 78.

(9) 3- and 4-OH-MBA were tentatively identified as metabolites of MBA without rigorous structural proof: Sims, P. *Biochem. J.* **1967**, *105*, 591.

(10) Harvey, R. G.; Sukumaran, K. B. *Tetrahedron Lett.* **1977**, 2387.

(11) (a) Harvey, R. G.; Urberg, K. *J. Org. Chem.* **1968**, *33*, 2206. (b) Harvey, R. G. *Synthesis* **1970**, 161. (c) Lindow, D. F.; Cortez, C. N.; Harvey, R. G. *J. Am. Chem. Soc.* **1972**, *94*, 5406.

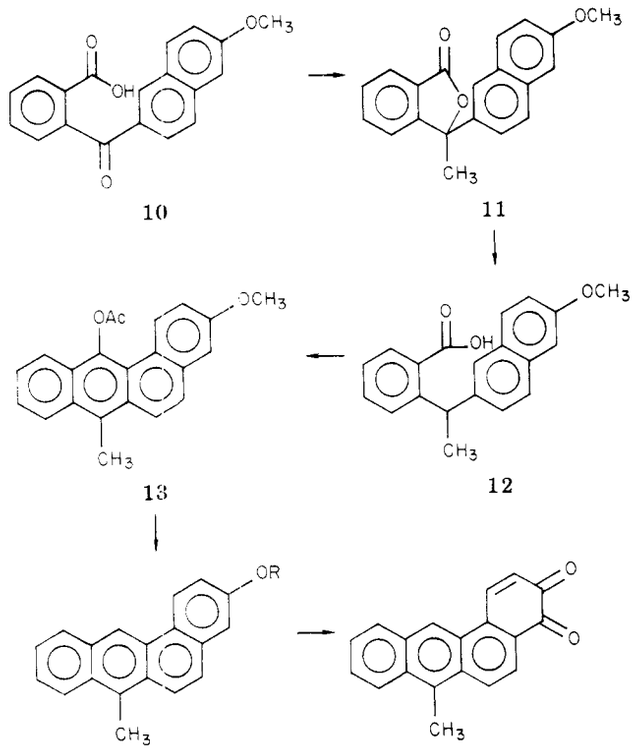
(12) Reduction of MBA with lithium in ammonia to 7,12-dihydro-7-methylbenz[a]anthracene has been described: Harvey, R. G.; Arzadon, L.; Grant, J.; Urberg, K. *J. Am. Chem. Soc.* **1969**, *91*, 4535.

(13) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.

(14) Bell, H. M.; Brown, H. C. *J. Am. Chem. Soc.* **1966**, *88*, 1463.

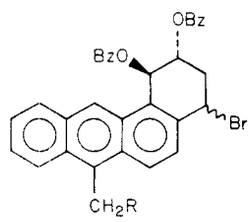
(15) Reduction of benzhydryl bromide with $NaBH_4$ in Me_2SO to afford substantial quantities of benzhydrol along with diphenylmethane is reported: Hutchins, R. O.; Hoke, D.; Keogh, J.; Koharski, D. *Tetrahedron Lett.* **1969**, 3495.

Scheme II



furnish the dibenzoate ester **1b**, which on treatment with NaOMe in methanol provided **1a**.

A similar sequence of transformations on **6b** furnished the isomeric trans 1,2-dihydro diol **3a** in 40% overall yield. The only low-yield step was methanolysis of **3b** which provided **3a** in 53% yield. Since methanolysis generally affords high yields of dihydro diols in other cases, it is likely the yield in this step can be improved. Surprisingly, reduction of the dibromo intermediate **9a** with $NaBH_4$ in either diglyme or Me_2SO afforded exclusively the 7-methyl-4-bromo derivative **9b**. The related 7-methyl-4-hydroxy compound was apparently not formed in Me_2SO, probably due to the relatively low reactivity of the 4-bromo compound.

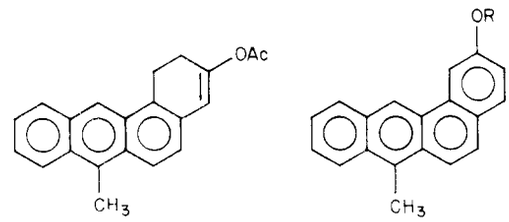


9a, R = Br
b, R = H

Epoxidation of the 3,4-dihydro diol with *m*-chloroperbenzoic acid afforded stereospecifically the corresponding anti diol epoxide **2**, while similar epoxidation of the 1,2-dihydro diol gave a mixture which showed one major component (80% by LC) which was trapped and identified by 270-MHz NMR as the anti isomeric diol epoxide **4a**. The syn isomer, which may be a minor product, could not be isolated on the small scale employed.

The alternative synthetic approach to **1a** outlined in Scheme II was explored when difficulties were experienced in developing a satisfactory procedure for selective reduction of **7**. This method involves synthesis of the key intermediate, 3-hydroxy-7-methylbenz[*a*]anthracene (**14b**), oxidation to the 3,4-quinone (**15**), and reduction. Reaction of the readily available[16] keto acid **10** with methylmagnesium bromide afforded the lactone **11** (90%), reduction of which with zinc and alkali gave the acid **12** (93%). Cyclization of **12** with $ZnCl_2$ and acetic anhydride[17] gave 12-acetoxy-3-methoxy-7-methylbenz[*a*]anthracene (**13**) (78%) which was deacetoxylated with zinc and alkali to 3-methoxy-7-methylbenz[*a*]anthracene (**14a**) (76%). Demethylation with sodium thioethoxide furnished the free phenol **14b** (97%). An alternative route to **14b** is described below. Oxidation of **14b** with Fremy's salt [$ON(SO_3K)_2$] gave violet crystals of 7-methylbenz[*a*]anthracene-3,4-dione (**15**) (91%). Reduction of the latter with LiAlH, furnished **1a** (15%). Lower yields than this are commonly encountered in reduction of terminal ring-*o*-quinones with $LiAlH_4$,[8a,18] and attempts to improve the yield of **1a** through variation in conditions or workup procedure were ineffectual.

The syntheses of 2- and 3-hydroxy-7-methylbenz[*a*]anthracene are based on the dibenzoate esters **6a,b**. Basic methanolysis of **6a** followed by acetylation with acetic anhydride–pyridine provided the corresponding diacetate ester **6c**. Acid-catalyzed elimination of the latter afforded the enol acetate **16** which underwent dehydrogenation with DDQ to afford 3-acetoxy-7-methylbenz[*a*]anthracene (**14c**). Treatment of the latter with methyllithium furnished the free phenol **14b** in good yield. 2-Hydroxy-7-methylbenz[*a*]anthracene (**17b**) was obtained from **6b** through an analogous sequence of transformations.



16

17a, R = Ac
b, R = H

Discussion

The syntheses of the trans 1,2-dihydro and trans 3,4-dihydro diols (**3a** and **1a**) of MBA and the corresponding diol epoxide derivatives (**4** and **2**) described herein provide relatively convenient synthetic approaches to these biologically important compounds. Since practical syntheses of the trans 5,6-dihydro and trans 10,11-dihydro diols of MBA have previously been described,[8a,21,22] four of the five possible dihydro diols of MBA are now available synthetically; the sole exception is the trans 8,9-dihydro diol.[7]

The two synthetic approaches to **1a** (Schemes I and II) each offer certain advantages. While the number of synthetic operations is approximately equivalent by both methods, the route from MBA affords the 1,2-dihydro diol and 2-hydroxy-7-methylbenz[*a*]anthracene with relatively few additional steps. On the other hand, the total synthetic approach via **10** has the merit of utilizing less costly and noncarcinogenic starting materials. Both methods

(16) Weizmann, C.; Bergmann, E.; Bergmann, F. *J. Chem. Soc.* **1935**, 1367.
(17) Smith, D. C. C. *J. Chem. Soc.* **1962**, 673.
(18) The sole exceptions are naphthalene-1,2-dione[19] and 7,12-dimethylbenz[*a*]anthracene-3,4-dione,[20] both of which are reported to afford good yields of the related trans dihydro diols.
(19) Booth, J.; Boyland, E.; Turner, E. E. *J. Chem. Soc.* **1950**, 1188.
(20) Sukumaran, K. B.; Harvey, R. G. *J. Am. Chem. Soc.* **1979**, *101*, 1353.
(21) Fu, P. P.; Harvey, R. G. *Tetrahedron Lett.* **1977**, 2059.
(22) Sims, P. *Biochem. J.* **1967**, *105*, 591.

provide good yields in all steps except the last. These methods are, therefore, complementary, the choice being dictated by the balance of the foregoing considerations.

The observed stereospecificity of epoxidation of **1a**, but not **3a**, is consistent with previous findings that anti-stereospecific epoxidation occurs only with trans dihydro diols free to adopt the diequatorial conformation.[8,23,24] Sterically crowded bay-region dihydro diols, such as **3a**, are shown by NMR[8b,24-26] and X-ray crystallographic evidence[26] to exist exclusively in the diaxial conformation both in solution and in the crystal lattice. Thus, $J_{1,2}$ = 2 Hz for **3a** is in good agreement with both the experimentally determined and theoretically calculated values for couplings between diequatorial protons of the diaxial conformers of molecules of this type.[26,27] The considerably larger value of $J_{3,4}$ = 12 Hz for **1a** is compatible with existence of this isomer predominantly in the diequatorial conformation.

Biological evidence supports the bay-region anti diol epoxide **2** as the ultimate carcinogenic form of MBA. Tumorigenicity experiments indicate **1a** to be more active as a carcinogen on mouse skin than MBA or the 1,2- or 5,6-dihydro diols.[5,28] The diol epoxide **2** exhibited only weak tumorigenic activity on mouse skin; tentatively, this is ascribed to indiscriminant interaction of this relatively reactive electrophile with proteins and other cellular components. The 3,4-dihydro diol also proved more mutagenic to *Salmonella typhimurium*[29] and more active in the induction of sister-chromatid exchange[30] than MBA or the isomeric dihydro diols. Investigation of the mutagenic activity of **1–4** in hamster V79 cells is currently in progress.

Experimental Section

General Notes. Benz[a]anthracene was obtained through reduction of benz[a]anthracene-7,12-dione with HI in acetic acid.[31] *N*-Bromosuccinimide (NBS) and 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) were supplied by Arapahoe Chemical Co.; NBS was crystallized from water prior to use. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) and *m*-chloroperbenzoic acid were purchased from Aldrich Chemical Co.; the peracid was purified by washing with pH 7.5 phosphate buffer and drying under reduced pressure. Methylmagnesium bromide, methyllithium, and potassium nitrosodisulfonate (Fremy's salt) were purchased from Alfa Ventron. THF and diglyme were distilled from $LiAlH_4$ prior to use. The NMR spectra were obtained on Varian T60 or Brucker HX270 spectrometers with tetramethylsilane as internal standard in $CDCl_3$ unless specified otherwise. Melting points are uncorrected. All new compounds gave satisfactory microanalyses for C and H within ±0.3% and/or mass spectra consistent with the assigned structure.

7-Methylbenz[a]anthracene. A mixture of benz[a]anthracene (11.4 g, 50 mmol) and NBS (10.6 g, 60 mmol) in 120 mL of CCl_4 was heated at reflux for 30 min, $FeCl_3 \cdot 6H_2O$ (50 mg) was added, and heating was continued for 1.5 h. The precipitate of succinimide was filtered off from the hot solution and washed with hot CCl_4. Methanol (10% of volume) was added to the hot filtrate which was concentrated by boiling to ~80 mL. The fine pale orange needles of 7-bromobenz[a]anthracene (11.38 g) melted at 150–151 °C (lit.[32] mp 147.5–148.5 °C). A second crop (1.78 g, mp 146–50 °C) was also obtained.

To a solution of 7-bromobenz[a]anthracene (4 g, 13 mmol) in 100 mL of anhydrous ether was added a solution of phenyllithium (26 mmol), and the resulting solution was heated at reflux for 15 min. Addition of methyl iodide (4.0 g, 28 mmol) decolorized the solution, which was stirred for an additional 10 min and then worked up conventionally to afford MBA (2.44 g), mp 135–136 °C; recrystallization from benzene–methanol gave a melting point of 138–139 °C (lit.[33] mp 140 °C).

Lithium–Ammonia Reduction of MBA. Reduction of MBA to 7,12-dihydro-7-methylbenz[a]anthracene was conducted according to the published procedure,[12] except that reaction was quenched with NH_4Cl as recommended in more recent publications,[11b,c] resulting in an improved yield (97%).

Reduction of 7,12-dihydro-7-methylbenz[a]anthracene (11.2 g, 46 mmol) with lithium (740 mg, 106 mmol) in THF (400 mL) and ammonia (400 mL) by the usual procedure,[10,11] quenching with NH_4Cl, gave **5**, isolated by chromatography on Florisil as an oil (11 g, 99%): NMR δ 1.38 (d, 3, CH_3), 3.39 (s, 4, $H_{1,4}$), 3.9 (m, 3, $H_{7,12}$), 5.89 (s, 2, $H_{2,3}$), 6.84–7.32 (m, 6, aromatic).

Isomerization of 5. A solution of **5** (22 g, 91 mmol) and NaOMe (7.3 g, 135 mmol) in degassed Me_2SO was stirred overnight at room temperature. The usual workup followed by chromatography on Florisil (hexane) afforded a mixture of tetrahydro-7-methylbenz[a]anthracene isomers (22.0 g): NMR δ 1.39 (m, 3, CH_3), 2.31 (br m, 2, allylic), 2.77 (apparent t, 2, benzylic), 3.97 (apparent d, 3, $H_{7,12}$), 5.77–6.58 (m, 2, vinylic), 6.59–7.40 (m, 6, aromatic). This product was employed directly in the following reaction.

Prévost Reaction of Tetrahydro-7-methylbenz[a]anthracene Isomers. A mixture of silver benzoate (49.5 g, 216 mmol) and I_2 (27.4 g, 108 mmol) in dry benzene (1 L) was stirred under reflux until the red color disappeared. A solution of the conjugated tetrahydro-7-methylbenz[a]anthracene isomers (22 g, 90 mmol) in dry benzene (200 mL) was added, and the resulting suspension was stirred at reflux for 16 h. The product was filtered hot and the precipitate washed with hot ethyl acetate. The combined filtrate was evaporated and the residue chromatographed on Florisil. Elution with hexane gave recovered tetrahydro-7-methylbenz[a]anthracene (3.8 g). Further elution with benzene furnished the mixed trans diol dibenzoates of 1,2,3,4,7,12-hexahydro-7-methylbenz[a]anthracene (35 g, 79%): NMR δ 1.48 (m, 3, CH_3), 2.31 (m, 2, CH_2), 3.01 (m, 2, CH_2), 3.91 (br s, 3, $H_{7,12}$), 5.59–6.51 (m, 2, CHOBz), 6.82–8.11 (m, 6, aromatic).

***trans*-1,2- and *trans*-3,4-Bis(benzoyloxy)-1,2,3,4-tetrahydro-7-methylbenz[a]anthracene (6a,b).** To a solution of the mixed dibenzoate esters from the previous reaction (35 g, 72 mmol) in dry benzene (1.2 L) under N_2 was added DDQ (18.2 g, 79.2 mmol) and the resulting solution was heated at reflux for 2.5 h. The hot solution was filtered through Celite, and the filtrate and benzene washes were evaporated and chromatographed on Florisil. Elution with benzene afforded pure **6a** (10 g) and a mixture of **6a** and **6b** (13 g). The latter were separated by fractional crystallization from ether. The less soluble isomer **6a** crystallized as white leaflets, mp 174–175 °C, while **6b** was obtained as pale yellow leaflets, mp 162–163 °C. The yields of pure **6a** and **6b** were 39% and 27%, respectively. NMR of **6a**: δ 2.51 (m, 2, H_2), 3.0 (s, 3, CH_3), 3.5 (apparent t, 2, H_1), 5.66 (m, 1, H_3), 6.65 (d, 1, H_4), 7.1–8.3 (m, 16, aromatic), 8.4 (s, 1, H_{12}). NMR of **6b**: δ 2.43 (m, 2, H_3), 3.03 (s, 1, CH_3), 3.05 (m, 2, H_4), 5.75 (m, 1, H_2), 6.95–8.5 (m, 17, aromatic).

***trans*-3,4-Bis(benzoyloxy)-3,4-dihydro-7-methylbenz[a]anthracene (1b).** A suspension of NBS (392 mg, 2.2 mmol) in a solution of **6a** (5.31 g, 1.1 mmol) and benzoyl peroxide (10 mg) in CCl_4 (150 mL) was heated at reflux for 1.5 h under N_2. Conventional workup afforded the crude dibromo derivative of **7** (700 mg, 99%) as a yellow solid: NMR δ 2.47–3.27 (m, 2, H_2), 5.33 (s,

(23) Although stereospecific epoxidation of the benzo[e]pyrene and triphenylene trans 9,10-dihydro diols was reported initially,[8b] subsequent reinvestigation in our laboratory has led to detection of lesser amounts of the syn isomer as a coproduct in variable ratio. Similar results have recently been obtained in the epoxidation of the 1,2- and 3,4-dihydro diols of chrysene.[24]

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(32) Badger, G. M.; Cook, J. J. *Chem. Soc.* **1949**, 409.

(33) Fieser, L.; Newman, M. S. *J. Am. Chem. Soc.* **1936**, *58*, 2376.

2, CH_2Br), 5.62–6.4 (m, 21, $H_{1,3}$), 6.8–8.9 (m, 18, H_4 and aromatic).

A suspension of **7** (900 mg, 1.4 mmol) and $NaBH_4$ (59 mg, 1.55 mmol) in freshly distilled diglyme (30 mL) was stirred at room temperature for 1.5 h. Workup gave **8a** (790 mg, 99%) as a yellow solid: NMR δ 2.83–3.8 (m, 2, H_2), 3.02 (br s, 3, CH_3), 5.7–6.41 (m, 2, $H_{1,3}$), 6.95–8.75 (m, 18, H_4 and aromatic).

To a solution of **8a** (790 mg, 1.4 mmol) in THF (150 mL) at 0 °C was added DBN (2 mL) dropwise. The resulting solution was stirred at 4 °C overnight. Workup afforded **1b** (454 mg, 67%) which on trituration with ether had a melting point of 221–223 °C: NMR (acetone-d_6) δ 3.03 (s, 3, CH_3), 6.18–6.93 (m, 3, $H_{2,3,4}$), 7.02–8.6 (m, 18, H_1 and aromatic).

Methanolysis of 1b. Treatment of **1b** with $NaOCH_3$ under the usual conditions[8a] (15 min reflux) gave **1a** (67 mg, 26%); physical properties were identical with those described for **1a** prepared via the alternative synthesis.

***trans*-1,2-Bis(benzoyloxy)-1,2-dihydro-7-methylbenz[*a*]anthracene (3b).** Dehydrogenation of **6b** (2 g, 4.1 mmol) through bromination with NBS and dehydrobromination with DBN was carried out by the procedures employed for the analogous reactions of **6a**. A similar workup afforded the dibromo derivative **9a** (2.64 g, 99%) as a yellow solid: NMR δ 2.92–3.11 (br m, 2, H_3), 5.44 (s, 2, CH_2Br), 5.64–5.91 (br m, 2, $H_{2,4}$), 7.08–8.74 (m, 18, H_1 and aromatic). Treatment of **9a** with $NaBH_4$ (171 mg, 4.5 mmol) in diglyme (250 mL) using a procedure similar to that employed for **7** furnished the monobromo derivative **9b** (2.3 g, 99%): NMR δ 2.85–3.09 (br m, 2, H_3), 3.01 (s, 3, CH_3), 5.61–5.97 (br m, 2, $H_{2,4}$), 7.0–8.5 (m, 18, H_1 and aromatic). Treatment of **9b** with DBN (7 mL) using a procedure similar to that employed for **8a** furnished **3b** (1.52 g, 77%): mp 112–114 °C; NMR δ 5.89 (d of d, 1, H_2), 6.43 (q, 1, H_3), 6.98 (d, 1, H_4), 7.05–8.75 (m, 18, H_1 and aromatic); $J_{1,2}$ = 2, $J_{2,3}$ = 5, $J_{3,4}$ = 9.5 Hz.

***trans*-1,2-Dihydroxy-1,2-dihydro-7-methylbenz[*a*]anthracene (3a).** Methanolysis of **3b** (1.52 g, 3.13 mmol) by the procedure employed for preparation of **1a** gave crude **3a**. Chromatography on Florisil (benzene–ethyl acetate, 3:1) furnished pure **3a** (471 mg, 53%) as a white solid: mp 171–173 °C; NMR (acetone-d_6 + D_2O) δ 3.02 (s, 3, CH_3), 4.48 (d of d, 1, H_2), 5.57 (d, 1, H_1), 6.16 (q, 1, H_3), 6.74 (d, 1, H_4), 7.17–8.36 (m, 6, aromatic), 9.84 (s, 1, H_{12}); $J_{1,2}$ = 2, $J_{2,3}$ = 6, $J_{3,4}$ = 9 Hz.

***trans*-3,4-Diacetoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (6c).** A solution of **6a** (1.58 g, 3.25 mmol) and 1 N NaOH (26 mL) in THF (75 mL) and methanol (140 mL) was stirred at room temperature for 3 h. Solvent was stripped off, cold water was added, and the precipitate of the crude tetrahydro diol (900 mg) was filtered off and dried. Acetylation with Ac_2O (50 mL) and pyridine (12 mL) at room temperature overnight gave **6c** (1.04 g, 89%) as a white solid: mp 169–170 °C; NMR δ 2.16 (s, 3, OAc), 2.04 (s, 3, OAc), 2.0–2.6 (m, 2, H_2), 3.01 (s, 3, CH_3), 3.2–3.54 (t, 2, H_1), 5.33 (q, 1, H_3), 6.26 (d, 1, H_4, $J_{3,4}$ = 6 Hz), 7.2–8.45 (m, 7, aromatic).

3-Acetoxy-1,2-dihydro-7-methylbenz[*a*]anthracene (16). A solution of **6c** (1.04 g, 2.9 mmol) and *p*-tosic acid (200 mg) in benzene (200 mL) was refluxed for 1.5 h. The solvent was then evaporated, isopropenyl acetate (200 mL) and Ac_2O (15 mL) were added, and the solution was refluxed overnight. Conventional workup followed by chromatography on Florsil (elution with benzene) afforded **16** (526 mg, 65%) as a white solid: mp 114–115 °C; NMR δ 2.2 (s, 3, OAc), 2.7 (t, 2, H_2), 3.55 (t, 2, H_1), 6.3 (s, 1, H_4), 7.06–8.4 (m, 7, aromatic).

3-Acetoxy-7-methylbenz[*a*]anthracene (14c). A solution of **16** (600 mg, 2 mmol) and *o*-chloranil (541 mg, 2.2 mmol) in benzene (100 mL) was refluxed for 1.5 h. Workup followed by chromatography on Florisil (elution with benzene) gave **14c** (316 mg, 53%) as a white solid: mp 142–143 °C; NMR δ 2.3 (s, 3, OAc), 2.89 (s, 3, CH_3), 7.1–8.28 (m, 8, aromatic), 8.6 (d, 1, H_1, $J_{1,2}$ = 8.5 Hz), 8.8 (s, 1, H_{12}).

3-Hydroxy-7-methylbenz[*a*]anthracene (14b). (a) From 14c. A suspension of **14c** (316 mg, 1.05 mmol) and methyllithium (3.15 mmol) in ether (50 mL) was stirred at room temperature for 1 h. Workup afforded **14b** (258 mg, 99%): mp 210–212 °C (benzene); NMR (acetone-d_6 + D_2O) δ 3.0 (s, 3, CH_3), 7.1–8.4 (m, 8, aromatic), 8.8 (d, 1, H_1, $J_{1,2}$ = 9 Hz), 9.1 (s, 1, H_{12}).

(b) From 14a. A solution of ethanethiol (4.9 g, 80 mmol) in dry DMF (35 mL) was added to a suspension of NaH (3.8 g of a 50% oil suspension) in DMF (25 mL) under N_2. After 5 min, a solution of **14a** (2.14 g, 8 mmol) in DMF (25 mL) was added, and the resulting suspension was stirred and heated at reflux for 3 h. The product was acidified with dilute HCl and worked up to afford **14b** (2 g, 97%) as a white solid: mp 210–212 °C; the NMR spectrum matched that above.

***trans*-1,2-Diacetoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (6d).** Alkaline hydrolysis of **6b** (2.05 g, 4.13 mmol) by the method employed for **6a** provided the corresponding tetrahydro diol (1.1 g) as a white solid. Acetylation with Ac_2O (20 mL) and pyridine (6 mL) overnight gave **6d** (1.37 g, 91%) as a white solid: mp 161–163 °C; NMR δ 2.0 (s, 3, OAc), 2.07 (s, 3, OAc), 2.15–2.4 (m, 2, H_3), 2.84–3.2 (m, 2, H_4), 3.03 (s, 3, CH_3), 5.4 (q, 1, H_2), 6.7 (d, 1, H_1, $J_{1,2}$ = 3.5 Hz), 7.1–8.35 (m, 7, aromatic).

2-Acetoxy-3,4-dihydro-7-methylbenz[*a*]anthracene. Acid-catalyzed dehydration of **6d** (3.15 g, 8.72 mmol) by the method employed for **6c** gave 2-acetoxy-3,4-dihydro-7-methylbenz[*a*]anthracene (2.1 g, 80%): mp 136–138 °C; NMR δ 2.13 (s, 3, OAc), 2.98 (s, 3, CH_3), 2.4–3.4 (m, 4, $H_{3,4}$), 7.1–8.45 (m, 8, H_1 and aromatic).

2-Acetoxy-7-methylbenz[*a*]anthracene (17a). Dehydrogenation of 2-acetoxy-3,4-dihydro-7-methylbenz[*a*]anthracene (1.4 g, 4.6 mmol) by the method used for **16** furnished **17a** (1.39 g, 99%): mp 170–172 °C; NMR δ 2.4 (s, 3, OAc), 3.01 (s, 3, CH_3), 7.13–8.53 (m, 9, aromatic), 8.9 (s, 1, H_{12}).

2-Hydroxy-7-methylbenz[*a*]anthracene (17b). Reaction of **17a** (265 mg, 0.88 mmol) with methyllithium (2.64 mmol) was carried out by the procedure employed for **14c** to obtain **17b** (220 mg, 99%) as a white solid: mp 178–179 °C; NMR (acetone-d_6 + D_2O) δ 2.99 (s, 3, CH_3), 7.01–8.4 (m, 9, aromatic), 9.07 (s, 1, H_{12}).

3-Methyl-3-(6-methoxy-2-naphthyl)phthalide (11). To a solution of *o*-(6-methoxy-2-naphthoyl)benzoic acid[16] (8.3 g, 2.75 mmol) in ether (500 mL) was added dropwise a solution of methylmagnesium bromide (6.9 mmol) in ether.[34] The resulting solution was heated at reflux overnight and worked up to afford **11** (7.5 g, 90%): mp 152–154 °C (ether); NMR δ 2.1 (s, 3, CH_3), 3.85 (s, 3, OCH_3), 6.97–7.97 (m, 9, aromatic).

***o*-[1-(6-Methoxy-2-naphthyl)ethyl]benzoic Acid (12).** A mixture of Zn dust (activated with 3 g of $CuSO_4$) and **11** (7.5 g, 24.8 mmol) in 800 mL of 10% KOH and 80 mL of pyridine[34] was heated at reflux overnight. The product was filtered and the filtrate acidified with dilute HCl. Extraction with ether followed by evaporation gave **12** (7 g, 93%): mp 207–209 °C (lit.[35] mp 207–208 °C); NMR δ 1.72 (d, 3, CH_3, J = 7 Hz), 3.88 (s, 3, OCH_3), 5.40 (q, 1, CH), 6.95–8.05 (m, 9, aromatic).

12-Acetoxy-3-methoxy-7-methylbenz[*a*]anthracene (13). The acid **12** (7 g, 23 mmol) and $ZnCl_2$ (400 mg) were heated in refluxing Ac_2O (60 mL) and AcOH (135 mL) for 1 h. Workup furnished **13** (5.9 g, 78%): mp 180–182 °C (benzene); NMR δ 2.51 (s, 3, OAc), 2.90 (s, 3, CH_3), 3.82 (s, 3, OCH_3), 7.02–8.38 (m, 8, aromatic), 9.08 (d, 1, H_1, $J_{1,2}$ = 10 Hz).

3-Methoxy-7-methylbenz[*a*]anthracene (14a). A mixture of zinc dust (150 g) activated with $CuSO_4$ (7 g)[34] and **13** (2 g) (6.06 mmol) in aqueous NaOH (70 g in 450 mL of H_2O) and dioxane (200 mL) was refluxed overnight. Workup[32] followed by trituration with benzene afforded **14a** (1.24 g, 76%): mp 165–167 °C; NMR δ 3.0 (s, 3, CH_3), 3.9 (s, 3, OCH_3), 7.1–8.28 (m, 8, aromatic), 8.66 (d, 1, H_1, $J_{1,2}$ = 10 Hz), 8.9 (s, 1, H_{12}).

7-Methylbenz[*a*]anthracene-3,4-dione (15). To a solution of Fremy's salt (7 g, 26 mmol) in $^1/_6$ M KH_2PO_4 buffer (60 mL) and H_2O (200 mL) was added a solution of **14b** (1.65 g, 6.4 mmol) in diglyme (60 mL). This mixture was stirred at room temperature for 1 h and then at 4 °C overnight. The purple quinone was filtered off, washed with water, and dried. Trituration with acetone–hexane provided pure **15** (1.58 g, 91%): mp 197–198 °C; NMR δ 3.08 (s, 3, CH_3), 5.59 (d, 1, H_2), 7.33–8.93 (m, 8, aromatic); IR ν_{max} 1663 (C=O) cm^{-1}.

***trans*-3,4-Dihydroxy-3,4-dihydro-7-methylbenz[*a*]anthracene (1a).** Reduction of **15** (200 mg, 0.7 mmol) with $LiAlH_4$ (150 mg, 4 mmol) in ether (200 mL) by the usual procedure (5 h) using a Soxhlet apparatus[8a,36] furnished **1a**. Trituration with

(34) Newman, M. S.; Sankaran, V.; Olson, D. R. *J. Am. Chem. Soc.* **1976**, *98*, 3237.
(35) Newman, M. S.; Khanna, J. M.; Khanna, V. K.; Kanakarajan, K. *J. Org. Chem.*, this issue.
(36) Cortez, C.; Harvey, R. G. *Org. Synth.* **1978**, *58*, 12.

ether gave pure **1a** (30 mg, 15%): mp 188–189 °C; NMR[7] (acetone-d_6 + D_2O) δ 3.04 (s, 3, CH_3), 4.38 (d of q, 1, H_3), 4.78 (d, 1, H_4), 6.08 (d of d, 1, H_2), 7.25–8.25 (m, 7, H_1 and aromatic), 8.73 (s, 1, H_{12}); $J_{1,2}$ = 10, $J_{2,3}$ = 3, $J_{3,4}$ = 12 Hz.

***trans*-3,4-Dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (2).** A solution of **1a** (23 mg, 0.083 mmol) and *m*-chloroperbenzoic acid (230 mg) in 25 mL of dry THF was stirred under N_2 for 2 h at room temperature. The solution was diluted with ether, washed twice with 10% aqueous NaOH solution and water, and dried. Evaporation of the solvent (avoiding heating), followed by trituration with ether, gave **2** (13 mg, 57%) as a white solid: mp 183–185 °C; NMR (acetone-d_6 + D_2O) 270 MHz δ 3.0 (s, 3, CH_3), 4.13 (q, 1, H_2), 4.31 (q, 1, H_3), 4.88 (d, 1, H_4), 5.40 (d, 1, H_1), 7.38–8.41 (m, 6, aromatic), 8.85 (s, 1, H_{12}); $J_{1,2}$ = 4.7, $J_{3,4}$ = 8.0, $J_{2,3}$ = 1.5 Hz.

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydro-7-methylbenz[*a*]anthracene (4a).** Epoxidation of **3a** (23 mg, 0.08 mmol) was carried out by the procedure employed for the analogous reactions of **1a**. Evaporation of the solvent (avoiding heating) gave crude **4a** (20 mg, 74%) which showed one major peak (80%) on LC on a Dupont Sil column (THF–heptane, 45:55). The major peak was collected and identified as **3a**: NMR (acetone-d_6 + D_2O) 270 MHz, δ 3.14 (s, 3, CH_3), 4.03 (d, 1, H_3), 4.28 (d, 1, H_4), 4.72 (br s, 1, H_2), 5.42 (apparent s, 1, H_1), 7.53–7.59 (m, 2, $H_{9,10}$), 7.75 (d, 1, H_5), 8.17 (d, 1, H_{11}), 8.37 (d, 1, H_8), 8.42 (d, 1, H_6), 8.82 (s, 1, H_{12}); $J_{1,2} \simeq 1$, $J_{2,3}$ = 0.98, $J_{3,4}$ = 3.73, $J_{5,6}$ = 8.96, $J_{8,9}$ = 8.11, $J_{10,11}$ = 8.63 Hz.

Acknowledgment. This investigation was supported by Grants CA 11968 and CA 14599 and research contract No. CP 033385 from the National Cancer Institute, DHEW. We also thank Professor Melvin S. Newman for his kind consent to delay publication of his related manuscript to permit simultaneous publication with this paper.

Registry No. **1a**, 64521-14-8; **1b**, 71988-88-0; **2**, 64625-66-7; **3a**, 64521-13-7; **3b**, 71988-89-1; **5**, 72016-70-7; **6a**, 71988-90-4; **6b**, 71988-91-5; **6c**, 71988-92-6; **6d**, 71988-93-7; **7**, 71988-94-8; **8a**, 71988-95-9; **9a**, 71988-96-0; **9b**, 71988-97-1; **10**, 71964-75-5; **11**, 71964-76-6; **12**, 71964-77-7; **13**, 71988-98-2; **14a**, 71988-99-3; **14b**, 71989-00-9; **14c**, 71989-01-0; **15**, 71989-02-1; **16**, 71989-03-2; **17a**, 71989-04-3; **17b**, 71989-05-4; 3,4,7,12-tetrahydro-7-methylbenz[*a*]anthracene, 71989-06-5; 1,2,7,12-tetrahydro-7-methylbenz[*a*]anthracene, 72016-71-8; 2-acetoxy-3,4-dihydro-7-methylbenz[*a*]anthracene, 72016-72-9; 7-methylbenz[*a*]anthracene, 2541-69-7; benz[*a*]anthracene, 56-55-3; 7-bromobenz[*a*]anthracene, 32795-84-9.

Hydride Transfer from 1,4-Dihydropyridines to sp^3-Hybridized Carbon in Sulfonium Salts and Activated Halides. Studies with NAD(P)H Models[1]

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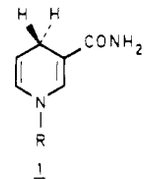
Received July 10, 1979

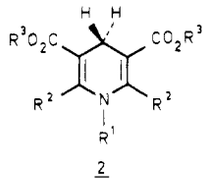
The reactions of 1,2,6-trimethyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (**2a**), 1-methyl-3,5-bis(methoxycarbonyl)-1,4-dihydropyridine (**2b**), and 1-benzyl-3-acetamido-1,4-dihydropyridine (**1**) with various sulfonium salts have been investigated. On thermal (60 °C) activation **2a,b** react with, for example, methylphenacylphenylsulfonium tetrafluoroborate (**3b**) to give the respective pyridinium salts, acetophenone, and phenyl methyl sulfide. There is some competing isomerization of the 1,4-dihydropyridines to their (nonreactive) 1,2-dihydro isomers, this being catalyzed by the pyridinium salt formed on reduction of the sulfonium salt. Phenacyl-, acetonyl-, and in some cases benzylsulfonium salts can be reduced. The group to which hydride transfer takes place should be electron deficient. These reductions can be initiated at room temperature with visible light (at room temperature pyridinium salt induced isomerization of the 1,4-dihydropyridine to its 1,2 isomer occurs only over a period of several days). The effect of visible light can be enhanced greatly by adding small amounts of dyes to the reaction mixtures. Eosin sodium salt, tetraphenylporphine, and $Ru^{II}(2,2'\text{-bpy})_3Cl_2$ are all capable of increasing the rate of reduction; the last dye is by far the most effective. The results of mechanistic investigations are consistent with the hypothesis that the light-induced reductions are one-electron transfer reactions. In some cases there appears to be a separate thermal mechanism not sensitive to either light or sensitizers. Some sulfonium salts react with dihydropyridines to give the pyridinium salt and sulfide in less than quantitative yield and no reduction products from the sulfonium salt. As determined for the case of the reaction of bromomalonitrile with **1**, and presumably also for other reactions, alkylation of an enamine carbon in the dihydropyridine is involved; the resulting iminium salt has been trapped by methanol and characterized.

The recognition that a 1,4-dihydronicotinamide (**1**) is the chemically active component of NAD(P)H[3] caused a surge of interest in 1,4-dihydropyridines in general. Derivatives of **1** are the most closely related in structure to the coenzyme. However, application of the tool of structural modification for mechanistic investigation is somewhat hampered for derivatives of **1**, owing to serious synthetic difficulties in obtaining such compounds.[4] A partial solution to this problem is found with the symmetrically substituted "Hantzsch esters" (**2**), which are readily synthesized with considerable variation in structure.



1

a) $CH_2C_6H_5$



2

a) $R^1 = R^2 = CH_3$; $R^3 = C_2H_5$

b) $R^1 = R^3 = CH_3$; $R^2 = H$

(1) Part 9 on the chemistry of dihydropyridines. For part 7 see R. H. van der Veen, R. M. Kellogg, A. Vos, and T. J. van Bergen, *J. Chem. Soc., Chem. Commun.*, 923 (1978); for part 8 see J. G. de Vries and R. M. Kellogg, *J. Am. Chem. Soc.*, **101**, 2759 (1979).

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