and 1,3-dimethyl-5-hydroxyhydantoin-5-*d* (**27**).

Ozonation of 1,3-Dimethyl-5-hydroxyhydantoin (9). Following the procedure for the ozonation of 1,3-dimethyluracil, 1,3-dimethyl-5-hydroxyhydantoin (0.1 g, 0.7 mmol) dissolved in water (5 mL) was allowed to react with ozone–oxygen. Following workup, the reaction mixture was subjected to gas chromatographic analysis. GC analysis revealed that only starting material, 1,3-dimethyl-5-hydroxyhydantoin, was present in the reaction mixture: t_r 11.27 min; coinjection with authentic sample, t_r 11.36 min (conditions B).

Preparation of 1,3,5-Trimethyluracil (28). Following the procedure for preparation of 1,3-dimethyluracil (**25**), 5-methyluracil (thymine, 10.0 g, 79.4 mmol), sodium hydroxide (7.5 g, 189 mmol), and dimethyl sulfate (23.3 g, 185 mmol) yielded 7.4 g (61%) of 1,3,5-trimethyluracil (**28**), mp 135–138 °C (lit.[25] mp 153 °C).

Ozonation of 1,3,5-Trimethyluracil (28). Following the above conditions for the ozonation of 1,3-dimethyluracil (**25**), a quantity of 1,3,5-trimethyluracil (1.0 g, 6.5 mmol) was allowed to react with ozone–oxygen (600 mL/min, 17 mg of O_3/min) for 45 min. The reaction mixture was analyzed by GC/MS (conditions C) to yield **methylpyruvamide (29)** (t_r 1.5 min) and **1,3,5-trimethyl-5-hydroxyhydantoin (30)** (t_r 7.2 min).

(25) T. B. Johnson and S. H. Clapp, *J. Biol. Chem.*, **5**, 49 (1908).

Acknowledgment. This work was supported by Environmental Protection Agency Grant R804472010. We thank R. T. Binder and R. A. Moore for laboratory assistance during this investigation. In addition, we thank the referees for many helpful suggestions.

Registry No. **1**, 58-08-2; **2**, 5176-82-9; **3**, 67646-19-9; **4**, 6726-48-3; **5**, 3659-97-0; **6**, 615-35-0; **7**, 22509-04-2; **8**, 824-28-2; **9**, 64732-10-1; **11**, 71194-98-4; **12**, 39832-36-5; **13**, 23043-88-1; **14**, 71194-99-5; **15**, 71195-00-1; **16**, 57012-86-9; **17**, 71195-01-2; **21**, 26351-03-1; **22**, 71195-02-3; **23**, 71195-03-4; **24**, 26351-04-2; **25**, 874-14-6; **26**, 40436-52-0; **27**, 71195-04-5; **28**, 4401-71-2; **29**, 19432-29-2; **30**, 71195-05-6; compound A, 10319-62-7; compound B, 71195-06-7; potassium isocyanate, 590-28-3; methyl isocyanate, 624-83-9; methylurea, 598-50-5; oxalyl chloride, 79-37-8; 5-azauracil, 71-33-0; theobromine, 83-67-0; ethyl iodide, 75-03-6; theophylline, 58-55-9; 1-ethyl-3-methyl-5-hydroxyhydantoin, 71195-07-8; 1-ethyl-3-methyl-5-azabarbituric acid, 71195-08-9; ethylurea, 625-52-5; dimethyl-d_6 sulfate, 15199-43-6; 1,7-dimethylxanthine, 611-59-6; uracil, 66-22-8; 5-methyluracil, 65-71-4; xanthine, 69-89-6; oxonic acid, 937-13-3; 1,3-dimethylurea, 96-31-1.

Supplementary Material Available: Spectroscopic data for **2–5**, **8**, **9**, **11–17**, **21**, **23–26**, and **28–30** (7 pages). Ordering information is given on any current masthead page.

Synthesis of the Dihydro Diols and Diol Epoxides of Chrysene from Chrysene

Peter P. Fu and Ronald G. Harvey*

Ben May Laboratory for Cancer Research, The University of Chicago, Chicago, Illinois 60637

Received February 13, 1979

Synthesis of the 1,2- and 3,4-trans dihydro diols (**1a** and **2a**) of chrysene and the corresponding anti isomeric diol epoxides (**3a** and **4**) is described. Synthesis of both **1a** and **2a** is accomplished in only seven steps from chrysene via initial hydrogenation over Adam's catalyst, dehydrogenation of the resulting 1,2,3,4-tetrahydrochrysene by NBS and DBN to a mixture (2:1) of 1,2- and 3,4-dihydrochrysene, Prévost reaction and chromatographic separation of isomers, followed by dehydrogenation and basic methanolysis of each isomer. An alternative regiospecific synthesis of **1a** involving initial hydrogenation of chrysene over a PtO_2–Pd/C catalyst to 1,2,3,4,5,6-hexahydrochrysene is also presented. These methods offer major advantages over established methods for the synthesis of polyarene dihydro diols which entail more complex multistep ring construction. NMR analysis indicates **1a** to exist preferentially in a diequatorial conformation, while **2a** is exclusively diaxially oriented. Epoxidation of **1a** affords stereospecifically the anti diol epoxide **3a**, whereas similar reaction of **2a** furnishes the corresponding anti and syn diol epoxides in a 5:3 ratio. Preliminary experiments indicate **3a** to be a potent inhibitor of the infectivity of ϕX174 DNA viral replication in *E. coli* spheroplasts, while **4** appears only weakly active.

Chrysene is a weak carcinogen and a widespread environmental contaminant.[1] It is present in the atmosphere, soil, marine sediments, automobile exhaust, smokestack effluents, cigarette smoke, and foods.[1,2] Recent research has implicated diol epoxide metabolites as the principal active forms of benzo[*a*]pyrene[3] and other carcinogenic polycyclic arenes.[4] Other evidence suggests that other types of active metabolites may also be involved.[5] In the case of chrysene, the 1,2- and 3,4-dihydro

(1) International Agency for Research on Cancer, "Monograph on the Evaluation of Carcinogenic Risk of the Chemical to Man: Certain Polycyclic Aromatic Hydrocarbons and Heterocyclic Compounds", Vol. 3. World Health Organization, Geneva, Switzerland, 1973, p 159.

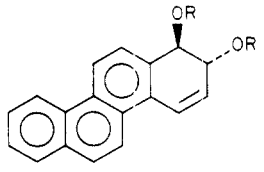
(2) E. J. Baum in "Polycyclic Hydrocarbons and Cancer: Environment, Chemistry, and Metabolism", Vol. 1, H. V. Gelboin and P. O. P. Ts'o, Eds., Academic Press, New York, N.Y., 1978, p 45.

(3) Reviews: (a) R. G. Harvey and P. P. Fu in ref 2, p 133; (b) E. C. Miller, *Cancer Res.*, **38**, 1479 (1978).

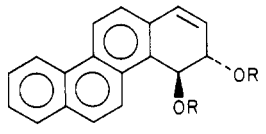
(4) T. J. Slaga, E. Huberman, J. K. Selkirk, R. G. Harvey, and W. M. Bracken, *Cancer Res.*, **38**, 1699 (1978); W. Levin, D. R. Thakker, A. W. Wood, R. L. Chang, R. E. Lehr, D. M. Jerina, and A. H. Conney, *ibid.*, **38**, 1705 (1978); C. Malaveille, B. Tierney, P. L. Grover, P. Sims, and H. Bartsch, *Biochem. Biophys. Res. Commun.*, **75**, 427 (1977); H. W. S. King, M. R. Osborne, and P. Brookes, *Int. J. Cancer*, **20**, 564 (1977); A. W. Wood, R. L. Chang, W. Levin, R. E. Lehr, M. Schaefer-Ridder, J. M. Karle, D. M. Jerina, and A. H. Conney, *Proc. Natl. Acad. Sci. U.S.A.*, **74**, 2746 (1977); V. Ivanovic, N. E. Geacintov, A. M. Jeffrey, P. P. Fu, R. G. Harvey, and I. B. Weinstein, *Cancer Lett.*, **4**, 131 (1978); P. Vigny, M. Duquesne, H. Coulomb, B. Tierney, P. L. Grover, and P. Sims, *FEBS Lett.*, **82**, 278 (1977); R. C. Moschel, W. M. Baird, and H. Dipple, *Biochem. Biophys. Res. Commun.*, **76**, 1092 (1977); A. W. Wood, W. Levin, P. E. Thomas, D. Ryan, J. M. Karle, H. Yagi, D. Jerina, and A. H. Conney, *Cancer Res.*, **38**, 1967 (1978); T. J. Slaga, G. L. Gleason, J. DiGiovanni, K. B. Sukumaran, and R. G. Harvey, *ibid.*, **39**, 1934 (1979).

0022-3263/79/1944-3778$01.00/0 © 1979 American Chemical Society

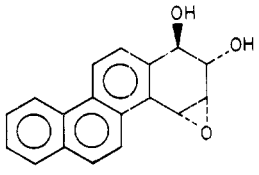
diols (**1a** and **2a**) have been tentatively identified as major products of metabolism in rat liver cells,[6] and the 1,2-dihydro diol has been demonstrated[7] to undergo metabolic activation by hepatic microsomes to a highly mutagenic metabolite presumed to be the anti and/or syn diol epoxide derivative (**3a,b**).[8]



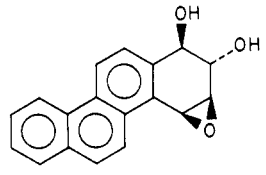
1a, R = H
b, R = Bz



2a, R = H
b, R = Bz

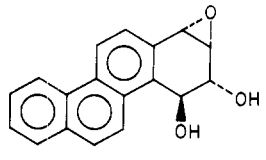


3a



3b

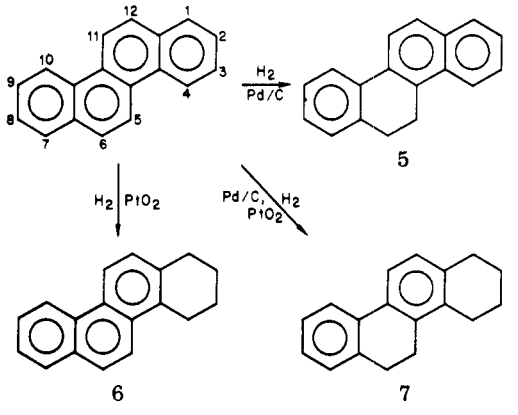
In a preliminary communication[9] we reported the synthesis of **3a** from chrysene via **1a** by a novel and convenient synthetic approach utilizing fewer steps than the conventional methods which involve complex multistep ring construction from smaller molecules.[3a,10] We now report full details of this method with application to the synthesis of both **3a** and the isomeric anti diol epoxide *trans*-3,4-dihydroxy-*anti*-1,2-epoxy-1,2,3,4-tetrahydrochrysene (**4**) derived from the 3,4-dihydro diol.



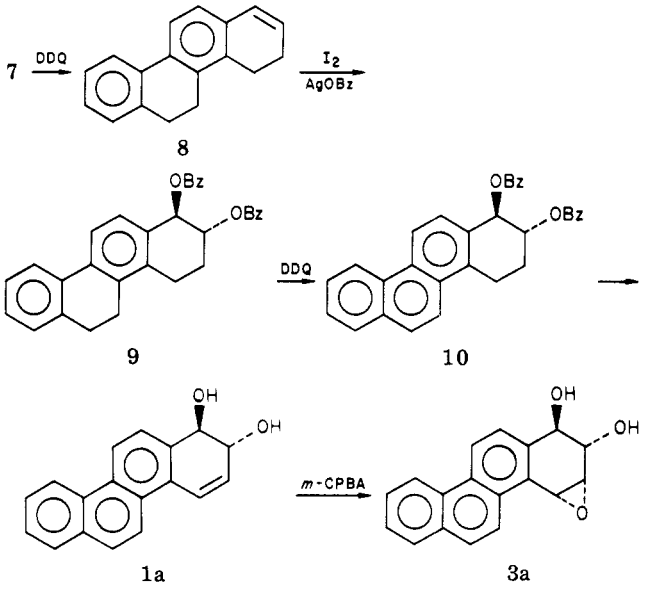
4

Development of convenient syntheses of the full range of oxidized metabolites of chrysene and other polycyclic arenes is seriously hampered by the deficiency of methods for the introduction of functional groups regioselectively into most positions of the polycyclic ring systems. Thus, substitution of chrysene by electrophilic reagents is known to take place predominantly in the 6-position.[11] The traditional solution to this problem has been laborious total syntheses of each isomeric derivative from appropriately substituted smaller molecular units.[11] Some preliminary approaches to the development of methods for the introduction of functional groups into positions not normally prone to direct substitution have been explored in the author's laboratory. One of these involves the use of halogen atoms as blocking groups to be removed at a later stage in synthesis.[12] A second approach involves regioselective hydrogenation either in the K region (Pd/C catalyst)[13] or in the terminal ring (Pt/C catalyst)[14] to afford useful polycyclic hydroaromatic intermediates potentially capable of undergoing reactions in benzylic or aromatic ring positions. The latter approach has been utilized in the synthesis of polycyclic dihydro arenes,[14] the synthetic precursors of the dihydro diols of polycyclic arenes.[3a] It is employed herein with appropriate modification for the synthesis of the necessary di- and tetrahydrochrysene intermediates.

Scheme I



Scheme II



Results

Hydrogenation of chrysene over a 10% Pd catalyst at low pressure (45 psig) afforded regiospecifically 5,6-dihydrochrysene (**5**), while similar reaction over PtO_2 gave 1,2,3,4-tetrahydrochrysene (**6**) along with several minor hydroaromatic products. Hydrogenation of chrysene over a mixed Pd/C–PtO_2 catalyst under similar conditions cleanly furnished 1,2,3,4,5,6-hexahydrochrysene (**7**) (Scheme I). These findings are in accord with the previously observed regioselectivities of these catalysts.[13,14]

(5) R. G. Harvey and F. B. Dunne, *Nature (London)*, **273**, 566 (1978).
(6) P. Sims, *Biochem. Pharmacol.*, **19**, 795 (1970). Structural assignments were based on UV spectra and TLC properties only and cannot, therefore, be considered as firmly established.
(7) A. W. Wood, W. Levin, D. Ryan, P. E. Thomas, H. Yagi, H. D. Mack, D. R. Thakker, D. M. Jerina, and A. H. Conney, *Biochem. Biophys. Res. Commun.*, **78**, 847 (1977).
(8) Compound **3a** is formally designated *trans*-1,2-dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrochrysene. The nomenclature of compounds of this type is currently in confusion because of the arbitrary use of different systems by various authors. The syn and anti terminology[3a] is preferred by the present authors because of its relatively greater simplicity and lack of ambiguity.
(9) P. P. Fu and R. G. Harvey, *J. Chem. Soc., Chem. Commun.*, 585 (1978).
(10) J. M. Karle, H. D. Mah, D. M. Jerina, and H. Yagi, *Tetrahedron Lett.*, 4021 (1977).
(11) E. Clar, "Polycyclic Hydrocarbons", Vol. I and II, Academic Press, New York, N.Y., 1964.
(12) R. G. Harvey and H. Cho, *J. Chem. Soc., Chem. Commun.*, 373 (1975).
(13) P. P. Fu and R. G. Harvey, *Tetrahedron Lett.*, **415** (1977).
(14) P. P. Fu, H. M. Lee, and R. G. Harvey, *Tetrahedron Lett.*, 551 (1978).

Table I. ^{1}H NMR Data[a] on the Dihydro Diols (1a, 2a), Dihydro Diol Dibenzoates (1b, 2b), Dibenzoates (1b, 2b), and Anti Diol Epoxides (3a, 4) of Chrysene

	δ				J, Hz	
	carbinol		vinylic or oxiranyl			
compd	benzylic (α′)	allylic (β′)	α[b]	β	$J_{\alpha,\beta}$	$J_{\alpha',\beta'}$
1a	4.92	4.41	7.30	6.20	10	10.5
1b	6.85	6.17		6.38	10	7.5
2a	5.43	4.40	6.70	6.22	9.5	2
2b		5.80	6.98	6.39	9.5	1.8
3a	4.63	3.90	4.99	3.76	4	8
4	5.18	4.22	4.06	3.90	4	8

[a] Spectra were taken on Varian T-60 and/or Bruker 270-MHz spectrometers in $CDCl_3$ (1b, 2b), acetone-d_6 (2a, 3b, 4), or acetone-d_6 + Me_2SO (1a, 3a) as specified; chemical shifts are in parts per million relative to Me_4Si. Diols were converted to their dideuterio derivatives by addition of D_2O to aid spectral interpretation. Further details of the spectra are presented in the Experimental Section. [b] α designates the vinylic or oxiranyl hydrogen adjacent to the aromatic ring system, i.e., H_1 or H_4, while β refers to the more distant hydrogen, i.e., H_2 or H_3, as appropriate.

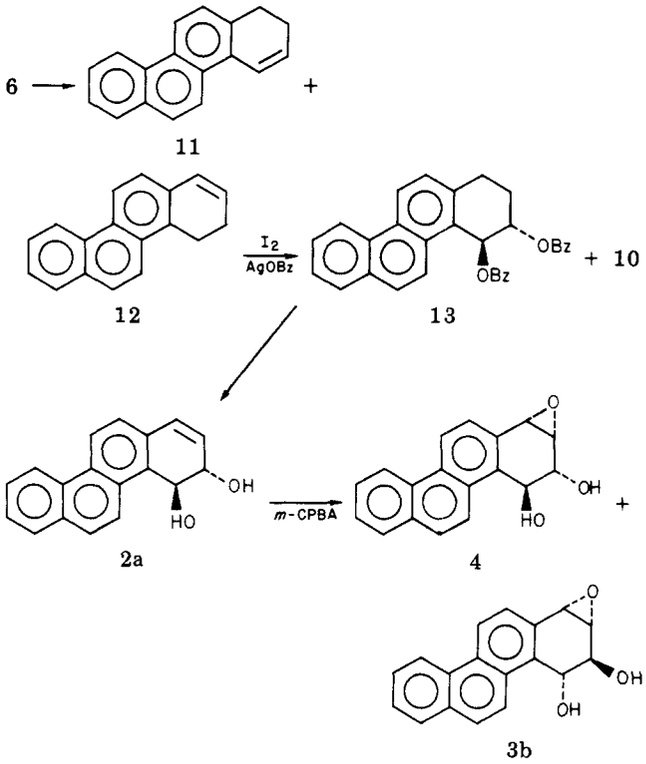
The tetrahydro- and hexahydrochrysene derivatives **6** and **7** were employed as intermediates in the synthesis of the 1,2- and 3,4-dihydro diols **1a** and **2a**.

Transformation of **7** to the 1,2-dihydro diol **1a** and the corresponding anti diol epoxide **3a** was accomplished via the reaction sequence depicted in Scheme II. Partial dehydrogenation of **7** with DDQ[13,15] in refluxing benzene took place regioselectively to provide 3,4,5,6-tetrahydrochrysene (**8**) accompanied by minor amounts of **5**, **6**, and chrysene. The alternative 1,2,5,6-tetrahydrochrysene isomer was not detected. Prévost reaction of this mixture of hydroaromatic chrysenes afforded *trans*-1,2-bis(benzoyloxy)-1,2,3,4,5,6-hexahydrochrysene (**9**). The latter was readily separated at this stage from chrysene and unreacted hydroaromatic chrysene derivatives by chromatography. Dehydrogenation of **9** with 2 equiv of DDQ[3a,13,15] in refluxing dioxane gave *trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene (**10**), mp 176–177 °C, in 91% yield. Further dehydrogenation to *trans*-1,2-bis(benzoyloxy)-1,2-dihydrochrysene (**1b**) failed to occur to a detectable extent over 3 days at 100 °C. However, dehydrogenation of **10** to **1b** was achieved through bromination with NBS[15,16] catalyzed by benzoyl peroxide followed by dehydrobromination with DBN. Treatment of **1b** with sodium methoxide in methanol furnished the 1,2-dihydro diol **1a** as a white solid, mp 266–267 °C. Finally, epoxidation of **1a** with *m*-chloroperbenzoic acid[3a] provided stereospecifically the anti diol epoxide **3a**.

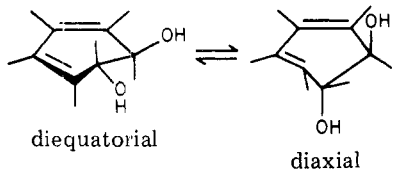
The integrated proton NMR spectra (Table I) of all compounds were in full agreement with the assigned structures. In particular, the H_4 protons of **1b**, **1a**, and **3a** exhibited the downfield shift characteristic of bay-region protons as a consequence of interaction with the adjacent H_5 aromatic proton. This feature distinguishes **1a**, **1b**, and **3a** from the isomeric compounds **2a**, **2b**, and **4** having the diol function in the bay region, since the NMR spectra of the latter (the synthesis of which is described in following paragraphs) do not exhibit a similar low-field displacement of the analogous vinyl and oxiranyl protons. In further confirmation of the isomeric structural assignments, the UV spectrum of **1a** matched that reported[10] for the 1,2-dihydro diol which differed markedly from that of the 3,4-dihydro diol.

Synthesis of the isomeric 3,4-trans dihydro diol **2a** and the corresponding anti diol epoxide **4** was accomplished from 1,2,3,4-tetrahydrochrysene via the reaction sequence depicted in Scheme III. The 1,2-trans dihydro diol is also obtainable by this method, which constitutes a relatively convenient synthetic route to both isomeric dihydro diols. Hydrogenation of chrysene over Adam's catalyst (50 psig, ambient temperature, 3 days) afforded crude 1,2,3,4-tetrahydrochrysene (**6**) purified by chromatography on a column of Florisil impregnated with 2% 2,4,7-trinitrofluorenone[17] and recrystallization; the pure **6** melted at 183–184 °C (lit.[18] mp 180 °C), and its NMR spectrum exhibited aromatic, benzylic, and aliphatic protons in the anticipated 2:1:1 ratio consistent with this structural assignment. Attempted partial dehydrogenation of **6** with DDQ furnished only chrysene and recovered **6**. However, bromination of **6** by NBS followed by dehydrobromination with DBN afforded a mixture of the isomeric 1,2- and 3,4-dihydrochrysenes (**11** and **12**). Prévost reaction of this mixture furnished the two diesters *trans*-3,4- and *trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene (**13** and **10**) in an approximately 2:1 ratio. The latter were readily separable from each other by chromatography. Conversion of **13** to **2a** was effected by the methods employed for the

Scheme III



(15) P. P. Fu and R. G. Harvey, *Chem. Rev.*, 78, 317 (1978).
(16) P. P. Fu and R. G. Harvey, *Tetrahedron Lett.*, 2059 (1977).
(17) R. G. Harvey and M. Halonen, *J. Chromatogr.*, **25**, 294 (1966).
(18) W. E. Bachmann and W. S. Struve, *J. Org. Chem.*, **4**, 456 (1939).



diequatorial diaxial

Figure 1. Conformational equilibrium of the 1,2-trans dihydro diol of chrysene (**2a**).

analogous conversion of **10** to **1a**. Dehydrogenation of **13** with NBS followed by dehydrobromination with DBN gave **2b** as a colorless solid, mp 86–87 °C (lit.[10] mp 86–87 °C). Treatment of the latter with sodium methoxide in methanol furnished the 3,4-dihydro diol, **2a**.

The structural assignments of **2a** and the intermediate dibenzoate esters **13** and **2b** are supported by the integrated NMR spectra (Table I). The spectrum of **2b** was also consistent with that reported by Karle et al.[10] for the authentic 3,4-dihydro diol diester. Comparison of the spectra of the 1,2- and 3,4-dihydro diol dibenzoates **1b** and **2b** reveals the anticipated downfield shift of the bay-region vinylic and benzylic protons due to the steric interaction in this crowded molecular region. A similar effect was also evident in the NMR spectra of the free dihydro diols. Thus, the H_4 benzylic signal of **2a** is found at δ 5.43, whereas the H_1 benzylic peak of **1a** appears at δ 4.92; correspondingly, the H_1 vinylic proton of **2a** is found at δ 6.70, while the analogous H_4 vinylic signal of **1a** is shifted downfield to δ 7.30. The UV spectrum of **2a** differed distinctively from that of **1a** and corresponded closely to that reported[10] for the chrysene 3,4-dihydro diol, further confirming the isomeric structural assignment.

The observed couplings between the benzylic and allylic protons of **1a** and **2a** and their diesters reveal an important conformational difference between the 1,2- and 3,4-dihydro derivatives. Thus, $J_{1,2}$ of **1a** and **1b** are 10.5 and 7.5 Hz, respectively, while $J_{3,4}$ of **2a** and **2b** are only 2.0 and 1.8 Hz, respectively. The latter values are in reasonably good agreement with the values of $J_{e,e'}$ = 2.8 Hz calculated on the basis of a dihedral angle of ~70° (from Drieding stereo models) between the equatorial protons of the diaxial conformer of **2a** (Figure 1) and the Karplus relationship as modified by Bothner-By.[19,20] Evidently, conformational interconversion is severely restricted by the strong steric interference to diequatorial orientation of the relatively bulky hydroxy or benzoyloxy groups by the bay-region aromatic ring. Consequently **2a** and **2b** apparently exist exclusively in the diaxial conformation. A diaxial conformational preference was noted earlier in the bay-region trans dihydro diols of benzo[*e*]pyrene,[21,22] triphenylene,[21] and phenanthrene.[23] In contrast, the analogous couplings of **1a** and **1b** ($J_{1,2}$ = 10.5 and 7.5 Hz, respectively) are intermediate between the calculated values of the diequatorial ($J_{e,e}$ = 2.8 Hz) and diaxial ($J_{a,a'}$ = 12.21 Hz) conformers, indicating existence of these isomers as an equilibrium mixture predominantly in the diequatorial conformation. The validity of conformational assignments of vicinal trans dihydro diols based upon NMR coupling

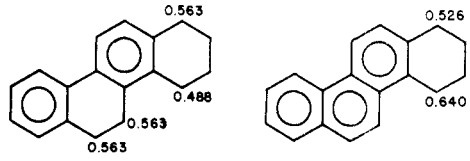


Figure 2. β-Delocalization energies (ΔE_{deloc}) in β units of the benzylic carbocations of 1,2,3,4,5,6-hexahydrochrysene (**7**) and 1,2,3,4-tetrahydrochrysene (**6**) calculated by the perturbational method of Dewar.[29,30]

constant data has recently been confirmed by X-ray crystallographic analysis of the 1,2- and 10,11-trans dihydro diols of benz[*a*]anthracene by Zacharias et al.[24]

Epoxidation of **2a** with *m*-chloroperbenzoic acid by the general procedure [3a] gave a mixture of the corresponding anti and syn diol epoxides **4** and **3b** in a 5:3 ratio. A similar lack of stereospecificity was observed during epoxidation of the diaxial benzo[*e*]pyrene 9,10-trans dihydro diol.[21] This finding contrasts with the observed anti stereospecific epoxidation of **1a**,[9] benzo[*a*]pyrene 7,8-trans dihydro diol,[3a,25] and the benz[*a*]anthracene 3,4-trans, 8,9-trans, and 10,11-trans dihydro diols,[3a,15,16,23,26] compounds known to exist predominantly in the diequatorial conformation. Evidently, as noted previously,[3a,21-23] anti stereospecific epoxidation occurs only with vicinal trans dihydro diols free to adopt the diequatorial conformation. Unfortunately, due to the facility of decomposition of most diol epoxides, it is generally not possible to separate the syn and anti isomers by chromatography or other conventional means without substantial decomposition.

Discussion

The syntheses of the terminal-ring dihydro diols and diol epoxides of chrysene outlined herein provide convenient synthetic methods for the preparation of these biologically important compounds from chrysene in relatively few steps. The 3,4-dihydro diol **2a** is obtainable from chrysene via the sequence outlined in Scheme III in five steps, and the 1,2-dihydro diol **1a** is obtainable from the intermediate **12** in three additional steps. Thus, both **2a** and **1a** are obtained from chrysene in a total of only seven steps overall. This contrasts with the conventional synthetic approaches[3a,10] to **1a** and **2a** from naphthalene[27] and phenanthrene,[18,28] respectively, via the intermediate ketones 1-oxo- and 4-oxo-1,2,3,4-tetrahydrochrysene which require a total of 22 synthetic operations. In principle, the synthetic method described herein should be generally applicable with appropriate modification to the synthesis of the dihydro diols and other oxidized metabolites of other carcinogenic hydrocarbons.

The regioselectivity of DDQ dehydrogenations has previously been found to be in accord with the rule that initial hydride abstraction occurs preferentially from the site affording the most stable carbonium ion,[14,15] pre-

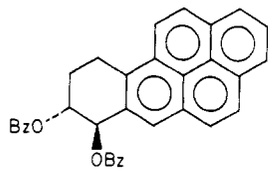
(19) A. A. Bothner-By, *Adv. Magn. Reson.*, 1, 195 (1965).
(20) R. G. Harvey, P. P. Fu, and P. W. Rabideau, *J. Org. Chem.*, 41, 3722 (1976).
(21) R. G. Harvey, H. M. Lee, and N. Shyamasundar, *J. Org. Chem.*, 44, 78 (1979). Only the *anti*-diol epoxide was isolated initially from epoxidation of benzo[*e*]pyrene-*trans*-9,10-dihydrodiol; however, subsequent repetition on a larger scale has led to detection of variable amounts of the syn isomer also formed in this reaction.
(22) R. E. Lehr, C. W. Taylor, S. Kumar, H. D. Mah, and D. M. Jerina, *J. Org. Chem.*, 43, 3462 (1978).
(23) R. E. Lehr, M. Schaefer-Ridder, and D. M. Jerina, *J. Org. Chem.*, 42, 736 (1977).
(24) D. Zacharias, J. P. Glusker, P. P. Fu, and R. G. Harvey, *J. Am. Chem. Soc.*, 101, 4043 (1979).
(25) F. A. Beland and R. G. Harvey, *J. Chem. Soc., Chem. Commun.*, 84 (1976).
(26) R. G. Harvey and K. B. Sukumaran, *Tetrahedron Lett.*, 2387 (1977).
(27) J. W. Cook and R. Schoental, *J. Chem. Soc.*, 288 (1945). Synthesis of 1-oxo-1,2,3,4-tetrahydrochrysene was accomplished through Friedel–Crafts succinoylation of naphthalene, Clemmensen reduction of the resulting keto acid, acid-catalyzed cyclization to 1-oxo-1,2,3,4-tetrahydrophenanthrene, Reformatski reaction, dehydration, dehydrogenation, and acid-catalyzed cyclization; separation of isomeric products is necessary at several stages.
(28) Synthesis of 4-oxo-1,2,3,4-tetrahydrochrysene from phenanthrene was achieved via catalytic hydrogenation to 9,10-dihydrophenanthrene, Friedel–Crafts succinoylation regioselectively in the 2-position, Clemmensen reduction, dehydrogenation, and acid-catalyzed cyclization.

dictable theoretically by MO methods.[29] The calculated β-delocalization energies of the benzylic carbocations of **7** are shown in Figure 2.[30] The values of ΔE_{deloc} are equivalent in the 1-, 5-, and 6-positions of **7** and these are higher than ΔE_{deloc} of the 4-position. In agreement with prediction, dehydrogenation is observed to take place preferentially in the 1-position to afford **8**, to a lesser extent in the 5-6-positions and to afford **6**, and to no detectable extent in the 4-position. The reason for predominance of **8** over **6** is not clear, except that steric inhibition may be expected to retard hydride abstraction at the 5-position. On similar grounds, dehydrogenation of 1,2,3,4-tetrahydrochrysene (**6**) is predicted to occur preferentially in the 4-position. Although dehydrogenation of **6** with DDQ could not be interupted at the dihydro stage, partial dehydrogenation was achieved by means of NBS bromination–dehydrobromination. Although the mechanism of this reaction presumably involves hydrogen radical abstraction,[31,32] product structure should be similarly predictable, since the calculated free valences of compounds of this type parallel ΔE_{deloc}. The major product of dehydrogenation is 1,2-dihydrochrysene (**11**), in accord with this expectation.

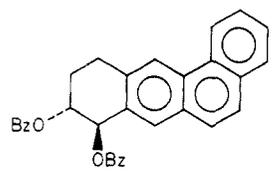
The failure of DDQ to dehydrogenate the tetrahydrochrysene dibenzoate **13** is apparently a consequence of the steric crowding in the bay region of this diester which forces the bulky benzoyloxy groups to adopt the transdiaxial conformation ($J_{3,4}$ = 3.0 Hz, consistent with this conformational assignment). Approach of the DDQ reagent is thereby seriously restricted from both molecular faces resulting in inhibition of hydrogen abstraction from the 1-position.[33] The reason for the failure of DDQ to dehydrogenate the isomeric 1,2-dibenzoate ester **10** is less clear. NMR analysis indicates the bulky diester groups to be oriented predominantly diequatorially ($J_{1,2}$ = 7.5 Hz), presenting minimal steric interference to approach of the reagent. While the related tetrahydrodibenzoates of benzo[*a*]pyrene (**15**) and benz[*a*]anthracene (**16**), also diequatorial, are readily dehydrogenated to the corresponding dihydrodibenzoates by DDQ, the isomeric tetrahydrodibenzoate of benz[*a*]anthracene (**17**) like **10** is resistant to this reagent,[3a,16] While the reasons for these differences are uncertain, it is clear that the facility of dehydrogenation by DDQ is highly sensitive to the structure of the compound undergoing reaction.

Biological Activity

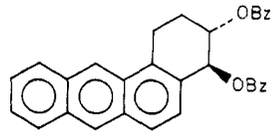
Preliminary experiments indicate the anti diol epoxide **3a** to be a potent inhibitor of the infectivity of ϕX174 DNA viral replication in *E. coli* spheroplasts[35] and a moderately active carcinogen on mouse skin;[36] the mixed isomeric *anti*- and syn 3,4-diol 1,2-epoxides exhibit only weak borderline activity in both respects. Also, the 1,2-dihydro diol **1a** is reported to be the most potent of the isomeric chrysene dihydro diols as a tumor initiator on the skins of female CD-1 mice.[37] These findings are in apparent accord with the "bay-region theory" which predicts that diol epoxides having the epoxide ring in a bay region should exhibit exceptional reactivity,[29,38] favoring their reaction with a critical cellular target, presumably DNA, leading to tumor induction.[39] On the other hand, chrysene is a particularly weak carcinogen, requiring promotion by phorbol esters for detectable activity.[1] This is apparently not a consequence of failure to undergo metabolism in the benzo ring, since both **1a** and **2a** are reported to be major metabolites of chrysene.[6] Full details of these and other biological studies are in progress and will be reported elsewhere.



15



16



17

Experimental Section

General Procedures. The PtO_2 and 10% Pd/C catalysts were purchased from Ventron Corp. *N*-Bromosuccinimide (NBS) and 2,4,7-trinitrofluorenone (TNF) were purchased from Eastman Chemicals, Inc.; NBS was recrystallized from water prior to use. 1,5-Diazabicyclo[4.3.0]non-5-ene (DBN) and *m*-chloroperbenzoic acid were obtained from Aldrich; the latter was purified by washing with pH 7.5 phosphate buffer and drying under reduced pressure.[41] Tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use.

The NMR spectra were obtained on Varian T60 or Bruker HX 270 spectrometers with tetramethylsilane as an internal standard in $CDCl_3$ unless specified otherwise. Hydrogenation experiments were conducted in a Vortex low-pressure hydrogenator manufactured by J. B. Thompson Co.; a 500-mL Pyrex bottle was used as the reaction vessel. 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 structures.

1,2,3,4,5,6-Hexahydrochrysene (7). Hydrogenation of chrysene (3.0 g, 13 mmol) was carried out over a mixed PtO_2 (440 mg)–10% Pd/C (573 mg) catalyst in acetic acid (20 mL) and ethyl acetate (20 mL) at 45 psig and ambient temperature for 3 days. The catalysts were removed by filtration through Celite and

(29) P. P. Fu, R. G. Harvey, and F. A. Beland, *Tetrahedron*, 34, 857 (1978).
(30) M. J. S. Dewar, "The Molecular Orbital Theory of Organic Compounds", McGraw-Hill, New York, N.Y.,1969, p 304-36.
(31) R. Filler, *Chem. Rev.*, 63, 21 (1963).
(32) J. S. Pizey, "Synthetic Reagents", Vol. II, Wiley, New York, N.Y., 1974, p 1.
(33) It has been suggested that "charge-transfer" complex formation may precede hydride abstraction during dehydrogenation of tetrahydroarenes by DDQ.[15] Since formation of molecular complexes is well established to be highly sensitive to steric effects,[34] it is possible that steric inhibition of complexation also contributes to retardation of dehydrogenation.
(34) R. Foster, "Organic Charge Transfer Complexes", Academic Press, New York, N.Y., 1969.
(35) W. T. Hsu, R. G. Harvey, E. J. Lin, and S. B. Weiss, *Proc. Natl. Acad. Sci. U.S.A.*, 74, 1378 (1977); W. T. Hsu, E. J. Lin, R. G. Harvey, and S. B. Weiss, *ibid.*, 74, 3335 (1977); W. T. Hsu, E. J. Lin, P. P. Fu, R. G. Harvey, and S. B. Weiss, *Biochem. Biophys. Res. Commun.*, 88, 251 (1979).
(36) T. J. Slaga, G. L. Gleason, G. Mills, L. Ewald, P. P. Fu, H. M. Lee, and R. G. Harvey, *Cancer Res.*, in press.
(37) W. Levin, A. W. Wood, R. L. Chang, H. Yagi, H. D. Mah, D. M. Jerina, and A. H. Conney, *Cancer Res.*, 38, 1831 (1978).
(38) D. M. Jerina, R. E. Lehr, H. Yagi, O. Hernandez, P. M. Dansette, P. G. Wislocki, A. W. Wood, R. L. Chang, W. Levin, and A. H. Conney in "In Vitro Metabolic Activation in Mutagenic Testing", Elsevier North-Holland Biomedical Press, Amsterdam, 1976, p 159.
(39) The theory fails to take into account structurally determined differences in the complex biological processes of enzymatic activation and concurrent detoxification, as well as steric effects, solubility differences, and other factors.[40] Moreover, it cannot account for the carcinogenic activity of hydrocarbons lacking a bay-region benzo ring or having substituents expected to block activation in this region.[5,40]
(40) R. G. Harvey in "Safe Handling of Chemical Carcinogens, Mutagens, and Teratogens: The Chemists Viewpoint", D. B. Walters, Ed., Ann Arbor Science Publishers, Inc., Ann Arbor, Mich., in press.
(41) N. N. Schwartz and J. H. Blumbergs, *J. Org. Chem.*, 29, 1976 (1964).

washed with ethyl acetate. The filtrate was evaporated to dryness, dissolved in a minimal volume of benzene, and chromatographed on a column (4 × 40 cm) of Florisil impregnated with 2% TNF.[17] Elution with hexane gave **7** (1.29 g, 42% yield, 70% based on chrysene conversion); recrystallization from benzene–hexane gave pure **7** as colorless needles: mp 112.5–113.5 °C; NMR (CCl_4) δ 1.60–1.97 (m, 4, $H_{2,3}$), 2.42–2.90 (m, 4, $H_{1,4}$), 2.73 (s, 4, $H_{5,6}$), 6.77–7.64 (m, 6, aromatic). Further elution with hexane gave a mixture (518 mg) of 1,2,3,4-tetrahydrochrysene (by NMR and TLC on TNF–silica gel[17]) along with several minor unidentified products. Finally, elution with benzene–hexane (1:4) provided recovered chrysene (1.2 g).

***trans*-1,2-Bis(benzoyloxy)-1,2,3,4,5,6-hexahydrochrysene (9).** A solution of **7** (630 mg, 2.7 mmol) and DDQ (630 mg, 2.7 mmol) in dry benzene (100 mL) was heated at reflux for 13 min. The initial deep red-brown solution became light yellow. The reaction mixture was filtered through a short column of neutral alumina eluted with benzene. Evaporation of the solvent left a white solid (550 mg) consisting mainly of 3,4,5,6-tetrahydrochrysene (**8**) identified by characteristic NMR peaks at δ (CCl_4) 2.2–2.5 (m, 2, H_3), 2.9–3.4 (m, 2, H_4), 5.75–6.15 (m, 1, H_2), and 6.45 (d, 1, $J_{1,2}$ = 9 Hz, H_1).

Prévost reaction was carried out directly on crude **8** without further purification since the main contaminants (**6**, **5**, and chrysene) were more easily separated from the product dibenzoate ester **9**. A solution of silver benzoate (2.29 g, 10 mmol) and I_2 (1.27 g, 5 mmol) in dry benzene (150 mL) was heated at reflux for 30 min. To this solution was added a solution of crude **8** (550 mg) in dry benzene (100 mL). The resulting solution was maintained at reflux for 2 days under N_2. The precipitate was removed by filtration through Celite, and the filtrate was chromatographed on a column (2.5 × 25 cm) of Florisil. Elution with hexane–benzenene (4:1) gave 202 mg of a mixture of **6** and **5** in the ratio of 4:1 (by NMR). Further elution with the same solvent and hexane–benzene (1:1) gave chrysene (33 mg). Elution with benzene gave **9** (682 mg, 53%) as a pale yellow solid: mp 164–165 °C (colorless prisms from benzene–hexane); NMR δ 2.16–2.53 (m, 2, H_3), 2.77 (s, 4, $H_{5,6}$), 2.63–3.12 (m, 2, H_4), 5.37–5.78 (m, 1, H_2), 6.57 (d, 1, $J_{1,2}$ = 6.5 Hz, H_1), 7.0–8.2 (m, 16, aromatic).

When crude **7** was employed directly in the synthesis of **9** via an otherwise analogous procedure, the overall yield of **9** from chrysene was 16% (28–30% based on chrysene conversion).

***trans*-1,2-Bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene (10).** Dehydrogenation of **9** (410 mg, 0.87 mmol) with DDQ (410 mg, 1.8 mmol) was carried out in refluxing dioxane (100 mL) under N_2 for 3 days. The reaction mixture was filtered through a short column of neutral alumina (2 × 10 cm). Elution with benzene furnished **10** (374 mg, 91%): mp 176–177 °C (colorless plates from acetone–hexane); NMR δ 2.37–2.70 (m, 2, H_3), 3.29–3.66 (m, 2, H_4), 5.45–5.83 (m, 1, H_2), 6.71 (d, 1, $J_{1,2}$ = 5 Hz, H_1), 7.13–8.17 (m, 16, aromatic), 8.43–8.83 (m, 2, $H_{10,11}$).

***trans*-1,2-Bis(benzoyloxy)-1,2-dihydrochrysene (1b).** Bromination of **10** (213 mg, 0.45 mmol) with NBS (82 mg, 0.46 mmol) was conducted in the presence of benzoyl peroxide (6 mg) in refluxing CCl_4 (30 mL) under N_2 for 20 min. Partition of the product between CCl_4 and water, followed by conventional workup, afforded 4-bromo-*trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene which was dehydrobrominated directly with DBN (1.2 equiv) in THF (10 mL) at room temperature overnight. Partition between ether and water followed by conventional workup gave crude **1b**. The latter was taken up in benzene and passed through a column of neutral alumina (2 × 10 cm) eluted with benzene and chromatographed on a 5% $AgNO_3$–Florisil column (2 × 10 cm). Elution with hexane–benzene (4:1) afforded **1b** (65 mg, 30%) as a light yellow solid: mp 173.5–175 °C (white solid from acetone); NMR δ 6.17 (dd, 1, $J_{1,2}$ = 7.5 Hz, $J_{2,3}$ = 3.5 Hz, H_2), 6.38 (dd, 1, $J_{2,3}$ = 3.5 Hz, $J_{3,4}$ = 10 Hz, H_3), 6.85 (d, 1, $J_{1,2}$ = 7.5 Hz, H_1), 7.15–8.20 (m, 17, aromatic and H_4), 8.41–8.70 (m, 2, $H_{10,11}$).

Repetition of this experiment twice under similar conditions provided **1b** in yields of 17 and 23%. Dehydrogenation by NBS bromination–dehydrobromination is notorious for its erratic nature.[15,16]

***trans*-1,2-Dihydroxy-1,2-dihydrochrysene (1a).** To a solution of **1b** (110 mg, 0.23 mmol) in dry THF (8 mL) was added sodium methoxide (26 mg, 0.48 mmol) in methanol (4 mL), and the resulting solution was heated at reflux under N_2 for 20 min. Conventional workup afforded **1a** (61 mg, 99%) as a white solid: mp 266–267 °C; NMR (acetone-d_6 + Me_2SO-d_6 (4:1) + 1 drop of D_2O) δ 4.41 (ddd, 1, $J_{1,2}$ = 10.5 Hz, $J_{2,3}$ = $J_{2,4}$ = 2 Hz, H_2), 4.92 (d, 1, $J_{1,2}$ = 10.5 Hz, H_1), 6.20 (dd, 1, $J_{2,3}$ = 2 Hz, $J_{3,4}$ = 10 Hz, H_3), 7.30 (dd, 1, $J_{3,4}$ = 10 Hz, $J_{2,4}$ = 2 Hz, H_4), 7.5–8.25 (m, 6, aromatic), 8.58–8.98 (m, 2, $H_{10,11}$).

***trans*-1,2-Dihydroxy-*anti*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (3a).** To a solution of **1a** (55 mg, 0.21 mmol) in freshly distilled THF (20 mL) was added a tenfold excess of *m*-chloroperbenzoic acid (378 mg). The solution was stirred at ambient temperature under N_2 for 1.5 h and then partitioned twice between ethyl ether and ethyl acetate and cold 10% NaOH solution as rapidly as possible. The organic layer was washed with cold water and dried over $MgSO_4$. Evaporation of the solvent and trituration three times with ether (0.5 mL each) afforded **3a** (48 mg, 82%) as a white solid: mp 225–227 °C (dec); NMR (acetone-d_6 + Me_2SO-d_6 + D_2O) δ 3.76 (d, 1, $J_{3,4}$ = 4 Hz, H_3), 3.90 (d, 1, $J_{1,2}$ = 8 Hz, H_2), 4.63 (dd, 1, $J_{1,2}$ = 8 Hz, $J_{2,3}$ = 2 Hz, H_1), 4.99 (dd, 1, $J_{2,3} \simeq$ 2 Hz, $J_{3,4}$ = 4 Hz, H_4), 7.95–8.11 (m, 2, $H_{8,9}$), 8.27–8.50 and 8.83–8.92 (m, 4, $J_{5,6}$ = $J_{11,12}$ = 10 Hz, $H_{5,6,7,12}$), 9.31 (t, 2, $H_{10,11}$).

1,2,3,4-Tetrahydrochrysene (6). Hydrogenation of chrysene (2.0 g, 8.8 mmol) was carried out over a PtO_2 catalyst (480 mg) in ethyl acetate (20 mL) at 50 psig and ambient temperature for 3 days. The catalyst was filtered off through Celite and washed several times with acetone–ethyl acetate. The residue remaining after evaporation of the solvent was dissolved in a small column of benzene and chromatographed on a column of 2% TNF impregnated on Florisil.[16] Elution with hexane gave a solid (572 mg) tentatively identified as a mixture of **7** and 1,2,3,4,7,8,-9,10-octahydrochrysene (by NMR). Further elution with hexane gave **6** (854 mg, 42%) as a white solid: mp 183–184 °C (benzene–ethanol) (lit.[18] mp 180.5–181.5 °C); NMR (CCl_4) δ 1.60–2.20 (m, 4, $H_{2,3}$), 2.65–3.30 (m, 4, $H_{1,4}$), 7.10–8.10 (m, 6, aromatic), 8.23–8.67 (m, 2, $H_{10,11}$).

***trans*-3,4- and *trans*-1,2-Bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene (13 and 10).** A solution of **6** (980 mg, 4.2 mmol), NBS (800 mg, 4.5 mmol), and benzoyl peroxide (10 mg) in CCl_4 (20 mL) was heated at gentle reflux for 25 min under N_2. The succinimide precipitate was filtered off and the solution evaporated to dryness. The residue was taken up in THF (15 mL), and the mixture was cooled to 0 °C overnight, partitioned between ether and water, washed with dilute HCl and water, dried ($MgSO_4$), and evaporated to dryness. The residue was chromatographed on a short column (2 × 10 cm) of Florisil eluted with hexane–benzene (9:1) to provide the mixed 1,2- and 3,4-dihydrochrysenes, **11** and **12** (638 mg).

Prévost reaction was carried out directly on the mixture of **11** and **12** under the same conditions employed for analogous reaction of **8** except the reaction period was shortened to 24 h. A similar workup procedure was employed. Chromatography of the product on Florisil gave on elution with benzene–hexane (1:9) a white solid (305 mg), identified as a mixture of **6** and chrysene (9:1) by NMR and TLC (TNF–silica gel) in comparison with authentic compounds (characteristic color and R_f value). Elution with benzene furnished **10** (229 mg) (by NMR and TLC comparison with authentic samples). Elution with 5% ethyl acetate in benzene provided **13** (389 mg) as a white solid: mp 120–121 °C (colorless needles from acetone–hexane) (lit.[10] mp 116–117 °C); NMR δ 2.28–2.62 (m, 3, H_2), 3.05–3.33 (m, 2, H_1), 5.70–5.90 (q, 1, H_3), 6.98 (d, 1, $J_{3,4}$ = 3 Hz, H_4), 7.17–8.05 (m, 16, aromatic), 8.52–8.85 (m, 2, $H_{10,11}$). The overall yield of **13** and **10** from **6** is 31%.

***trans*-3,4-Bis(benzoyloxy)-3,4-dihydrochrysene (2b).** Dehydrogenation of **13** (360 mg) was accomplished by NBS bromination–DBN dehydrobromination, using essentially the procedure employed for dehydrogenation of **10**. Compound **2b** was obtained as a colorless solid (151 mg): mp 86–87 °C (lit.[10] 86–87 °C); NMR δ 5.80 (dd, 1, $J_{2,3}$ = 5 Hz, $J_{3,4}$ = 1.8 Hz, H_3), 6.39 (dd, 1, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 5 Hz, H_2), 6.98 (d, 1, $J_{1,2}$ = 9.5 Hz, H_1), 7.0–8.0 (m, 19, H_4 and aromatic), 8.40–8.80 (m, 2, $H_{10,11}$).

***trans*-3,4-Dihydroxy-3,4-dihydrochrysene (2a).** Methanolysis of **2b** (140 mg, 0.41 mmol) with $NaOCH_3$ in methanol, following a procedure analogous to that employed for similar reaction of **1b**, gave **2a** (100 mg, 92%) as a white solid: mp 187–190 °C; NMR (acetone-d_6) δ 4.40 (dd, 1, $J_{2,3}$ = 5 Hz, $J_{3,4}$ = 2 Hz, H_3),

5.43 (apparent d, 1, $J_{3,4}$ = 2 Hz, H_4), 6.22 (dd, 1, $J_{1,2}$ = 9.5 Hz, $J_{2,3}$ = 5 Hz, H_2), 6.70 (d, 1, $J_{1,2}$ = 9.5 Hz, H_1), 7.36-8.33 (m, 6, aromatic), 8.55–8.88 (m, 2, $H_{10,11}$).

***trans*-3,4-Dihydroxy-*anti*- and -*syn*-3,4-epoxy-1,2,3,4-tetrahydrochrysene (4 and 3b).** A solution of **2a** (37 mg, 0.014 mmol) and *m*-chloroperbenzoic acid (250 mg) in dry THF (15 mL) was stirred at ambient temperature for 30 min under N_2. The resulting solution was partitioned between ethyl acetate and cold 10% NaOH solution (2 × 80 mL), and the organic layer was washed with water (100 mL), dried ($MgSO_4$), and evaporated to dryness (ambient temperature) to afford a mixture of the anti and syn isomeric diol epoxides (18 mg, 46%) in the ratio of 5:3. NMR of the anti isomer (acetone-d_6–D_2O) δ 3.90(m, 1, H_2), 4.06 (m, 1, H_1), 4.22 (m, 1, H_3), 5.18 (m, 1, H_4), $J_{3,4}$ = 8 Hz, $J_{2,3}$ = 1–2 Hz, $J_{1,2} \simeq$ 4 Hz; NMR of the syn isomer δ 4.22 (m, 1, H_2), 4.35 (m, 1, H_1), 4.67 (m, 1, H_3), 5.37 (m, 1, H_4) (coupling constants were too difficult to estimate accurately on the small amount of this component present).

Acknowledgment. This investigation was supported by Grants CA 11968 and CA 14599 and a research contract (CP 033385) from the National Cancer Institute, DHEW.

Registry No. **1a**, 64920-31-6; **1b**, 69303-41-9; **2a**, 64920-32-7; **2b**, 66267-16-1; **3a**, 64938-66-5; **3b**, 64920-33-8; **4**, 70951-83-6; **5**, 2091-92-1; **6**, 2091-90-9; **7**, 2091-91-0; **8**, 69104-29-6; **9**, 69104-30-9; **10**, 69275-38-3; **11**, 18930-98-8; **12**, 71435-43-3; **13**, 66267-12-7; chrysene, 218-01-9; 1,2,3,4-tetrahydrochrysene, 2091-90-9; 4-bromo-*trans*-1,2-bis(benzoyloxy)-1,2,3,4-tetrahydrochrysene, 71435-44-4; 1,2,3,4,7,8,9,10-octahydrochrysene, 2091-87-4.

New Synthetic Approach to 4-Alkylidenecyclohexenes. Reduction–Protodesilylation of Benzylsilanes

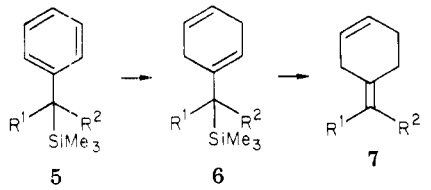
Daniel J. Coughlin and Robert G. Salomon*

Department of Chemistry, Case Western Reserve University, Cleveland, Ohio 44106

Received March 28, 1979

Synthetic methodology is described which allows conversion of benzylsilanes into 4-alkylidenecyclohexenes or 4-alkylidenecyclohexanones in good yields. Structurally specific syntheses are readily achieved for various derivatives which are not efficiently accessible by conventional methods. These include the natural product, terpinolene, as well as 2-methyl-4-methylenecyclohexan-1-one and 3-carbomethoxy-5-methylenecyclohex-1-ene.

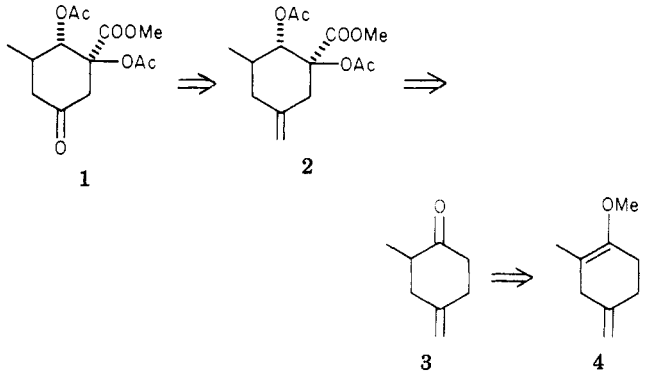
Alkylidenecyclohexyl structures are ubiquitous in natural products. Alkylidenecyclohexanones are important rudimentary synthons for elaboration of natural products.[1] In connection with our studies on leucogenenol,[2] we envisioned synthetic applications of 4-methylenecyclohexanones which exploit the C=C unit as a latent carbonyl.[4] This is illustrated in a projected synthesis of ketone **1**, the structure proposed for a keto triester obtained from a hydrolytic fragment of leucogenenol.[5] Thus, the retrosynthetic analysis shown in Scheme I uses an olefin **2** as the penultimate target. Our interest in developing an efficient synthesis of the key intermediate **3**, and recognition that this ketone could be obtained from the enol ether **4**, provided the impetus to demonstrate a synthetic equivalency of 4-alkylidene-1-cyclohexenes **7** and benzylsilanes **5**. Thus, (3,6-dihydrobenzyl)silanes **6**,



5 **6** **7**

obtained from benzylsilanes **5** by Birch reduction,[6] should

Scheme I



1 **2** **3** **4**

afford **7** by protodesilylation.[7] Electrophilic substitution of the allylic silicon in **6** by a proton was expected to occur regiospecifically with transposition of an endocyclic C=C bond into the desired exocyclic position.[7,8] The present study demonstrates the feasibility and explores the scope of this new synthetic method.

Results

Synthesis of Benzylsilanes. A representative selection of primary, secondary, and tertiary benzylsilanes was prepared by replacement of a benzylic halogen or hydrogen with a trimethylsilyl group by several methods. Thus benzylsilanes **5a–e** (Table I) were prepared by in situ

(1) For some examples including nootkatone, isonootkatone, and perfume compositions see: Marshall, J. A.; Ruden, R. A. *J. Org. Chem.* **1971**, *36*, 594. Marshall, J. A.; Warne, T. M. *Ibid.* **1971**, *36*, 178; Swiss Patent 554934, 1975; *Chem. Abstr.* **1975**, *82*, 98214.

(2) Leucogenenol is a natural product which functions as a hormone in regulating the rate of maturation and transformation of blood cells[3a] and which facilitates antibody production.[3b]

(3) (a) Rice, F. A. H. *J. Infect. Dis.* **1968**, *118*, 76. Rice, F. A. H.; Darden, J. H. *Ibid.* **1968**, *118*, 289. (b) Rice, F. A. H.; Lepick, J.; Darden, J. H. *Radiat. Res.* **1968**, *36*, 144. Rice, F. A. H.; Lepick, J.; Hepner, P. *Ibid.* **1970**, *42*, 164.

(4) For reviews see: Lednicer, D. *Adv. Org. Chem.* **1972**, *8*, 179. Evans, D. A.; Andrews, G. C. *Acc. Chem. Res.* **1974**, *7*, 147. Seebach, D.; Enders, D. *Angew. Chem., Int. Ed. Engl.* **1975**, *14*, 15.

(5) Rice, F. A. H. *J. Chem. Soc. C* **1971**, 2599. Rice, F. A. H. *Carbohydr. Res.*, **1972**, *21*, 65.

(6) Eaborn, C.; Jackson, R. A.; Pearce, R. *J. Chem. Soc., Perkin Trans. 1* **1975**, 470.

(7) Fleming, I. *Chem. Ind. (London)* **1975**, *7*, 449.

(8) (a) Somi, A. H.; Sakurai, H. *Tetrahedron Lett.*, **1976**, 1295. (b) Carter, M. J.; Fleming, I., *J. Chem. Soc., Chem. Commun.* **1976**, 679. (c) Calas, R.; Dunogues, J.; Pillot, J.-P.; Biran, C.; Pisciotti, F.; Arreguy, B. *J. Organomet. Chem.* **1975**, *85*, 149. (d) Deleris, G.; Dunogues, J.; Calas, R. *Ibid.* **1975**, *93*, 43. (e) Au-Yeung, B.-W.; Fleming, I. *J. Chem. Soc., Chem. Commun.* **1977**, *79*. (f) Frainnet, E. *Bull. Soc. Chim. Fr.* **1959**, 1441. (g) Wilson, S. R.; Phillips, L. R.; Natalie, K. J., Jr. *J. Am. Chem. Soc.* **1979**, *101*, 3340.

0022-3263/79/1944-3784$01.00/0 © 1979 American Chemical Society