Absolute Configuration of the 9,10-Epoxides of 9,10,11,12-Tetrahydrobenzo[e]pyrene: Application of the Exciton Chirality Rule to the p-Methoxybenzoate of a Bromohydrin

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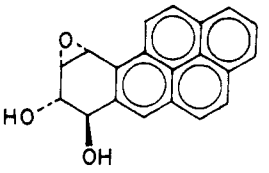
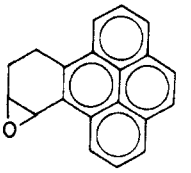
Resolution of the highly mutagenic (±)-9,10-epoxide of 9,10,11,12-tetrahydrobenzo[e]pyrene (BePE) and assignment of the absolute configurations of the individual enantiomers is described. The diastereomeric (−)-menthoxyacetate ester derivatives of (±)-*trans*-10-bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[e]pyrene (**1b**) were separated on preparative scale by HPLC on silica gel. Treatment of (+)- and (−)-**1b** with sodium methoxide gave directly optically pure (−)- and (+)-BePE, respectively. Contrary to previous observations with other diastereomeric (−)-menthoxyacetate esters of analogous bromohydrin derivatives, the NMR spectra failed to reveal significant differences in the exocyclic methylene protons that could be correlated with the absolute configurations. The absolute stereochemical assignments of the resolved bromohydrin enantiomers were accomplished by their conversion into the corresponding *p*-methoxybenzoate esters and application of the exciton chirality circular dichroism method of Nakanishi. This direct method is operationally simpler and more convenient than the indirect methods previously employed for analogous bromohydrins.

Covalent interaction of reactive metabolites with nucleic acids has been implicated as a critical step in the mechanism of carcinogenesis of polycyclic aromatic hydrocarbons.[1,2] The active metabolite of benzo[a]pyrene has been identified as (+)-*trans*-7,8-dihydroxy-*anti*-9,10-epoxy-7,8,9,10-tetrahydrobenzo[a]pyrene [(+)-*anti*-BPDE], and covalent binding of this intermediate with DNA and RNA has been shown to take place principally on the exocyclic amino group of guanosine via trans addition to the epoxide ring.[1,2] Kinetic studies indicate that intercalation of (+)-*anti*-BPDE between the base pairs of the DNA helix precedes formation of the covalent DNA adduct.[3,4]

It has also become increasingly evident that stereochemical and structural factors importantly influence the reaction pathways of PAH epoxides with nucleic acids. Thus, while reaction of (+)-*anti*-BPDE with DNA is essentially regiospecific, analogous reaction of (−)-*anti*-BPDE affords a more complex mixture of PAH–DNA adducts.[5] In contrast, the racemic 9,10-epoxides of 7,8,9,10-tetrahydrobenzo[a]pyrene (BaPE) and 9,10,11,12-tetrahydrobenzo[e]pyrene (BePE), which lack hydroxyl groups, both react with DNA mainly on the 2-NH_2 group of guanine predominantly via cis addition to the epoxide ring.[6]



(+)-anti-BPDE



BePE

Regioselectivity of attack is apparently dependent upon chiral interaction of the hydroxyl groups with DNA. While the enantiomers of BaPE react to approximately equal extent with DNA, alkylation of guanosine sites in DNA by racemic BePE takes place stereospecifically with only one of the enantiomers.[6] The configuration of the active enantiomer and the molecular basis of this remarkable steric preference are unknown.

The present report describes resolution of BePE and assignment of the absolute configuration of the individual enantiomers. The method employed is novel, involving application of the exciton chirality rule[7] to the *p*-methoxybenzoate of the bromohydrin precursor of BePE. The availability of the optically pure (+) and (−) enantiomers of BePE permits determination of the absolute configuration of the enantiomer of BePE that binds selectively to DNA and determination of the relationship between binding and biological activity.

Two basic methods have been employed previously for the resolution of the epoxide, dihydrodiol, and related oxidized metabolites of PAH. One of these (method A) entails separation of the mixture of diastereomeric (−)-menthoxyacetate or other appropriate diester derivatives of a dihydro- or a tetrahydrodiol by fractional crystallization or chromatographic methods (HPLC in more recent studies), followed by hydrolysis and conversion of the individual resolved diols to the desired compounds by methods that conserve stereochemical integrity. The second approach (method B) involves separation of the pair of diastereomeric esters of the appropriate bromohydrin intermediate, followed by hydrolysis, cyclization to the epoxide, and conversion to the desired compounds.

(1) Reviews: (a) Harvey, R. G. *Acc. Chem. Res.* **1981**, *14*, 218. (b) Weinstein, I. B.; Jeffrey, A. M.; Leffler, S.; Pulkrabek, P.; Yamasaki, H.; Grunberger, D. In "Polycyclic Hydrocarbons and Cancer"; Gelboin, H. V., Ts'o, P. O. P., Eds.; Academic Press: New York, 1978; Vol. 2.

(2) King, H. W. S.; Osborne, M. R.; Beland, F.; Harvey, R. G.; Brookes, P. *Proc. Natl. Acad. Sci. U.S.A.* **1976**, *73*, 2679. Weinstein, I. B.; Jeffrey, A. M.; Jennette, K.; Blobstein, S.; Harvey, R. G.; Harris, C.; Autrup, H.; Kasai, H.; Nakanishi, K. *Science (Washington, D.C.)* **1976**, *193*, 592. Jeffrey, A. M.; Jennette, K. W.; Blobstein, S. H.; Weinstein, I. B.; Beland, F. A.; Harvey, R. G.; Kasai, H.; Muira, I.; Nakanishi, K. *J. Am. Chem. Soc.* **1976**, *98*, 5714. Jennette, K. W.; Jeffrey, A. M.; Blobstein, S. H.; Beland, F. A.; Harvey, R. G. *Biochemistry* **1977**, *16*, 932. Straub, K. M.; Meehan, T.; Burlingame, A. L.; Calvin, M. *Proc. Natl. Acad. Sci. U.S.A.* **1977**, *74*, 5285. Koreeda, M.; Moore, P. D.; Wislocki, P. G.; Levin, W.; Conney, A. H.; Yagi, H.; Jerina, D. M. *Science (Washington, D.C.)* **1978**, *199*, 778.

(3) Geacintov, N. E.; Ibanez, V.; Benjamin, M. J.; Hibshoosh, H.; Harvey, R. G. In "International Symposium on Polynuclear Aromatic Hydrocarbons", 7th, Battelle Laboratories: Columbus, OH, 1983. Geacintov, N. E.; Yoshida, H.; Ibanez, V.; Harvey, R. G. *Biochemistry* **1982**, *21*, 1864.

(4) Drinkwater, N. R.; Miller, J. A.,; Miller, E. C.; Yang, N. C. *Cancer Res.* **1978**, *38*, 3247. Hogan, M. E.; Dattagupta, N.; Whitlock, J. P. *J. Biol. Chem.* **1981**, *256*, 4504.

(5) Osborne, M. R.; Jacobs, S.; Harvey, R. G.; Brookes, P. *Carcinogenesis* **1981**, *2*, 553.

(6) Kinoshita, T.; Lee, H. M.; Harvey, R. G.; Jeffrey, A. M. *Carcinogenesis* **1982**, *3*, 255.

(7) Harada, N.; Nakanishi, K. *J. Am. Chem. Soc.* **1969**, *91*, 3989. Harada, N.; Nakanishi, K. *Acc. Chem. Res.* **1972**, *5*, 257. Harada, N.; Chen, S. L.; Nakanishi, K. *J. Am. Chem. Soc.* **1975**, *97*, 5345.

0022-3263/84/1949-1114$01.50/0

In method A, absolute stereochemical assignments are generally accomplished by conversion of the resolved dihydro- or tetrahydrodiol enantiomers to their *p*-(dimethylamino)benzoate or other appropriate diesters and application of the exciton chirality circular dichroism method of Nakanishi.[7] In method B, absolute stereochemical assignments are most frequently made by either (i) reduction of the optically pure epoxide with a metal hydride reagent to a monoalcohol or (ii) hydrolysis of the individual epoxide enantiomers to the corresponding dihydrodiols followed by esterification to the appropriate mono- or dibenzoate ester and application of the exciton chirality rule. Method A has been utilized to resolve oxidized derivatives of benz[*a*]anthracene,[8] benzo[*c*]phenanthrene,[9] chrysene,[8b] benzo[*a*]pyrene,[10] and phenanthrene.[11] Method B has been used to separate derivatives of naphthalene,[12] anthracene,[12] phenanthrene,[13] chrysene,[8b] benz[*a*]anthracene,[14] and benzo[*a*]pyrene.[15]

Results and Discussion

The optically pure enantiomers of BePE were prepared by a modification of method B. The bromohydrin derivative of BeP, (±)-*trans*-10-bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (**1a**), was obtained from reaction of 9,10-dihydrobenzo[*e*]pyrene with *N*-bromosuccinimide in moist dimethyl sulfoxide and converted to its menthoxyacetate ester **1b** by treatment with (−)-menthoxyacetyl chloride. The diastereomeric (−)-menthoxyacetates were separated by HPLC on silica gel on preparative scale. The (−) diastereomer, (−)-**1b**, had $[\alpha]^{23}_D$ −219° ($CHCl_3$), while the more polar (+) isomer, (+)-**1b**, had $[\alpha]^{23}_D$ +109° ($CHCl_3$).

The NMR spectra of the diastereomeric (−)-menthoxyacetates failed to reveal any significant differences in the splitting pattern of the exocyclic methylene protons that could be correlated with the absolute configurations of the individual diastereomers. The CH_2 protons in the acetyl group appeared as a pair of doublets, δ 4.14 and 4.09 (J = 16.5 Hz) in (−)-**1b**, and δ 4.15 and 4.08 (J = 16.6 Hz) in (+)-**1b**, indicative of the nonequivalence of the H_A and H_B methylene protons of both diastereomers. This finding contrasts with the previous reports that the exocyclic methylene protons of the analogous bromomenthoxyacetate derivatives of naphthalene,[12] anthracene,[12] phenanthrene,[13] benz[*a*]anthracene,[14] chrysene,[8a] and benzo[*a*]pyrene[16] appear as an AB quartet in the more polar diastereomer and as a singlet in the less polar diastereomer. In all these reported cases the absolute configuration of the diastereomer that exhibited nonequivalence of the acetate CH_2 protons was found to be *S,S*. It was suggested, therefore, that the splitting of H_A and H_B may have diagnostic significance for predicting the absolute configurations of bromomenthoxyacetate esters.[12] However, the present finding that both diastereomers of **1b** exhibit magnetic nonequivalence of methylene protons indicates that this correlation is not general. Further contrary evidence is provided by the NMR spectra of the diastereomers of the (−)-menthoxyacetate of (±)-*trans*-9-bromo-10-hydroxy-7,8,9,10-tetrahydrobenzo[*a*]pyrene in both of which the CH_2 protons also appear as a pair of doublets.[16] It appears, therefore, that absolute configurational assignments of these diastereomeric bromohydrin derivatives cannot be made reliably on the basis of NMR spectral analysis.

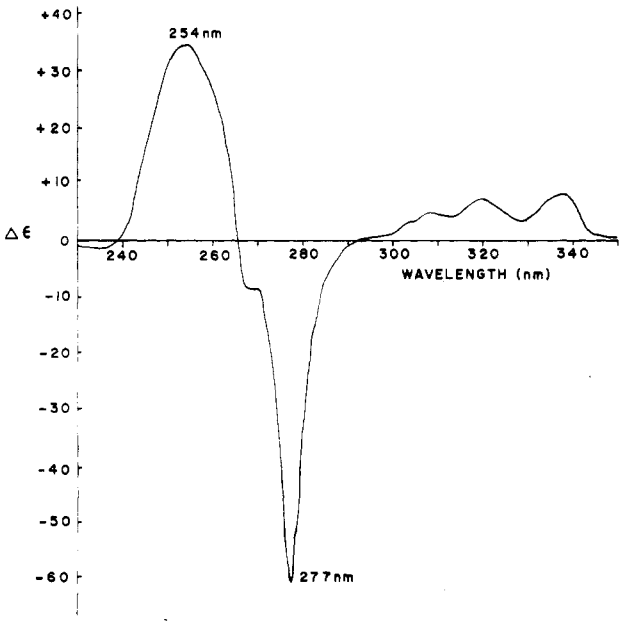


Figure 1. Circular dichroism spectrum of the *p*-methoxybenzoate ester of (+)-*trans*-10-bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene, (+)-**1a**, recorded in ethanol. The negative band at 277 nm and the positive band at 254 nm requires the 9*S*,10*S* absolute configuration.

Cyclization of the optically pure diastereomers of **1b** to the corresponding epoxides, (+)- and (−)-BePE, was accomplished directly by treatment with sodium methoxide. Prior reductive cleavage of the menthoxyacetate esters with diborane[8b,14] was unnecessary. The (−) diastereomer of **1b** gave (+)-BePE and (+)-**1b** provided (−)-BePE.

The absolute configuration of the enantiomeric epoxides was assigned by application of the exciton chirality method. Deesterification of (+)-**1b** with $LiAlH_4$ gave smoothly the optically pure (+)-bromohydrin, (+)-**1a**. Esterification of (+)-**1a** with *p*-methoxybenzoyl chloride in pyridine furnished the corresponding *p*-methoxybenzoate ester **1c**. The circular dichroism spectrum of this ester (Figure 1) showed a negative first Cotton effect centered at 277 nm and a positive second Cotton effect at 254 nm. The negative sign of the longest wavelength Cotton effect indicates that the chirality between the long axes of the pyrene and the *p*-methoxybenzoate chromophores is negative, from which the absolute configuration is deduced to be 9*S*,10*S*. On this basis the 9*S*,10*S* con-

(8) (a) Levin, W.; Thakker, D. R.; Wood, A. W.; Chang, R. L.; Lehr, R. E.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1978**, *38*, 1705. (b) Yagi, H.; Vyas, K. P.; Tada, M.; Thakker, D. R.; Jerina, D. M. *J. Org. Chem.* **1982**, *47*, 1110. (c) Yang, S. K. *Drug Metab. Disp.* **1982**, *10*, 205. Chou, M. W.; Chiu, P.; Fu, P. P.; Yang, S. K. *Carcinogenesis* **1983**, *5*, 629.

(9) Yagi, H.; Thakker, D. R.; Ittah, Y.; Croisy-Delcey, M.; Jerina, D. M. *Tetrahedron Lett.* **1983**, *24*, 1349.

(10) (a) Harvey, R. G.; Cho, H. *Anal. Biochem.* **1977**, *80*, 540. (b) Yang, S. K.; Gelboin, H. V.; Weber, J. D.; Sankaran, V.; Fischer, D. L.; Engel, J. F. *Ibid.* **1977**, *78*, 520. (c) Yang, S. K.; Roller, P. P.; Gelboin, H. V. *Biochemistry* **1977**, *16*, 3680. (d) Thakker, D. R.; Yagi, H.; Akagi, H.; Koreeda, M.; Lu, A. Y.; Levin, A.; Wood, A. W.; Conney, A. H.; Jerina, D. M. *Chem.-Biol. Interact.* **1977**, *16*, 281. (e) Kedzierski, B.; Thakker, D. R.; Armstrong, R. N.; Jerina, D. M. *Tetrahedron Lett.* **1981**, *22*, 405.

(11) Vyas, K. P.; Thakker, D. R.; Levin, W.; Yagi, H.; Conney, A. H.; Jerina, D. M. *Chem.-Biol. Interact.* **1982**, *38*, 203.

(12) Aktar, M. N.; Boyd, D. R.; Hamilton, J. G. *J. Chem. Soc., Perkin Trans. 1* **1979**, 2437.

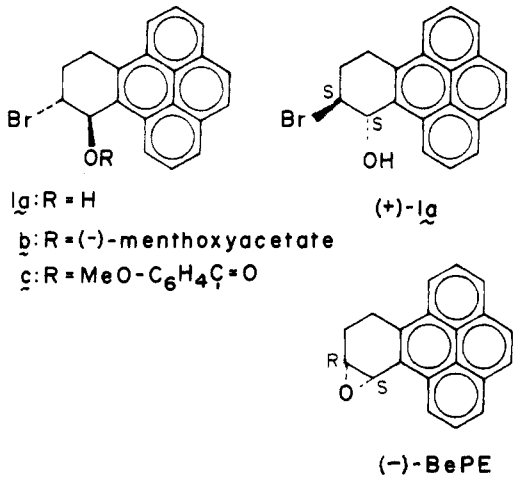
(13) Boyd, D. R.; Neill, J. D.; Stubbs, M. E. *J. Chem. Soc., Chem. Commun.* **1977**, 873. Koreeda, M.; Aktar, M. N.; Boyd, D. R.; Neill, J.; Gibson, D.; Jerina, D. M. *J. Org. Chem.* **1978**, *43*, 1023.

(14) Boyd, D. R.; Dawson, K. A.; Gadaginamath, G. S.; Hamilton, J. G.; Malone, J. F.; Sharma, N. D. *J. Chem. Soc., Perkin Trans. 1* **1981**, 94. Boyd, D. R.; Gadaginamath, G. S.; Sharma, N. D.; Drake, A. F.; Mason, S. F.; Jerina, D. M. *Ibid.* 2233.

(15) Boyd, D. R.; Gadaginamath, G. S.; Kher, A.; Malone, J. F.; Yagi, H.; Jerina, D. M. *J. Chem. Soc., Perkin Trans. 1* **1980**, 2112.

(16) Harvey, R. G.; Lee, H., unpublished studies.

figuration may be assigned to the corresponding (+)-bromohydrin, (+)-**1a**, and the 9*S*,10*R* configuration to the related epoxide, (-)-BePE. The CD spectrum of the *p*-methoxybenzoate ester of the (-)-bromohydrin was essentially the mirror image of its enantiomer (+)-**1c**, confirming the optical purity of the resolved bromohydrins and the absolute configuration of (-)-**1a** as 9*R*,10*R* and (+)-BePE as 9*R*,10*S*.



1a: R = H (+)-**1a**

b: R = (-)-menthoxyacetate

c: R = MeO-C_6H_4C=O

(-)-BePE

The method of absolute stereochemical assignment of bromohydrin enantiomers reported herein is operationally simpler and more convenient than the less direct methods previously employed for other bromohydrins.[8b,12-15] In the present procedure, the resolved bromohydrins are converted directly into the appropriate benzoate ester derivatives for stereochemical assignment by the exciton chirality method. In previous methods, the resolved bromohydrins were initially converted into the enantiomeric epoxides, which were then either (i) reduced with $LiAlH_4$ to the corresponding monoalcohol, which was converted to a monobenzoate ester, or (ii) hydrolyzed and esterified to a dibenzoate ester, which was then utilized to assign the absolute configuration. Both of these procedures require a greater number of steps, each of which may furnish variable amounts of secondary products including other stereoisomeric products.[17] The method reported herein is inherently free of these difficulties and would appear to be the method of choice wherever it is applicable.

A linear dichroism study of the covalent adducts formed by the reactions of the two enantiomers of BePE with DNA indicates that (+)-BePE reacts to greater extent than (-)-BePE, but the conformations of the adducts are qualitatively similar.[18] Both enantiomers of BePE give rise to site I (quasi-intercalated) and site II (externally bound) adducts. This finding contrasts with the marked differences observed earlier in the adducts formed by (+)- and (-)-*anti*-BPDE where the (+) enantiomer formed almost pure site II adduct and (-)-*anti*-BPDE gave a mixture of site I and II adducts.[19] Evidently the configuration of the hydroxyl groups of BPDE plays an important role in determining the nature of adducts formed on covalent binding to DNA.

Biological studies show BePE to be highly mutagenic to Chinese hamster V79 cells and to strains TA98 and TA100 of Salmonella typimurium.[20] BePE was nontumorigenic in the newborn mouse at low dosage; testing at higher levels was prevented by its extreme toxicity.[21] Indirect evidence for the tumorigenicity of BePE is provided by 9,10-dihydrobenzo[*e*]pyrene, the metabolic precursor of BePE, which exhibited significant activity as a tumor initiator on mouse skin.[22] Investigations of the biological properties of (+)- and (-)-BePE are in progress and will be reported elsewhere.

Experimental Section

General Methods. The NMR spectra were recorded on a Varian EM-360 and/or The University of Chicago 500-MHz spectrometers in $CDCl_3$ with tetramethylsilane as internal standard; only selected signals are reported. Specific rotations were measured on a Perkin-Elmer 141 automatic polarimeter. The CD spectra were recorded on a Cary 60 spectrophotometer. (-)-Menthoxyacetyl chloride was prepared from (-)-menthoxyacetic acid (Aldrich Chemical Co.) as described.[23] 9,10-Dihydrobenzo[*e*]pyrene was synthesized by the method reported.[24] All new compounds gave satisfactory microanalysis for C, H within ±0.3%. Melting points are uncorrected. *N*-Bromosuccinimide (Aldrich) was recrystallized from water and tetrahydrofuran (THF) was distilled from $LiAlH_4$ prior to use.

(±)-*trans*-10-Bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene (1a). 9,10-Dihydrobenzo[*e*]pyrene[24] (1 g, 4 mmol) and NBS (783 mg, 4.4 mmol) were added to dimethyl sulfoxide (100 mL) containing 1 mL of H_2O, and the mixture was stirred at room temperature for 1 h under N_2. The product was partitioned between ether and water, and the ether layer was dried over $MgSO_4$ and evaporated to dryness. The residue was recrystallized from $CHCl_3$ to yield **1a** (1.4 g, >99%) as a white solid: mp 150–151 °C; NMR δ 2.5 (m, 2, H_{11}), 3.5 (m, 2, H_{12}), 4.8 (m, 1 H_{10}), 5.8 (m, 1, H_9), 8.1–8.7 (m, 8, Ar). The use of excess NBS, longer reaction time, or N-bromoacetamide in place of NBS all resulted in lower yield.

(+)- and (-)-*trans*-10-Bromo-9-(menthoxyacetoxy)-9,10,11,12-tetrahydrobenzo[*e*]pyrene (1b). To a solution of **1a** (700 mg, 2.0 mmol) in pyridine (10 mL) was added (-)-menthoxyacetyl chloride (1 g) dropwise at 0 °C, and the resulting solution was stirred overnight at ambient temperature. The usual workup followed by chromatography on a column of Florisil eluted with benzene gave the mixed diastereomeric menthoxyacetates **1b** (1.08 g, 99%) as an oil. Preparative HPLC separation of the diastereomers of **1b** (850 mg) was achieved on a 10-μm silica gel column (7 mm × 50 cm × 6) eluted with THF–hexane (3:2) at a flow rate of 10 mL/min. Evaporation of the early fractions gave the less polar diastereomer (-)-(9*R*,10*R*)-**1b** as a white solid (407 mg, >99% optically pure): mp 154–155 °C (EtOAc); $[\alpha]^{23}_D$ -219° (0.5 g/100 mL, $CHCl_3$); NMR (500 MHz) δ 4.14 and 4.09 (dd, 2, $COCH_2$, J_{gem} = 16.5 Hz), 4.84 (d, 1, H_{10}, $J_{10,11}$ = 2.6 Hz), 7.03 (d, 1, H_9, $J_{9,10}$ = 1.2 Hz), 8.00–8.18 (m, 6, Ar), 8.24 (d, 1, H_1, $J_{1,2}$ = 7.7 Hz), 8.42 (d, 1, H_8, $J_{7,8}$ = 7.8 Hz). Evaporation of the later fractions afforded the more polar diastereomer (+)-(9*S*,10*S*)-**1b** as a white solid (395 mg, >99% optically pure); mp 157–159 °C (EtOAc); $[\alpha]^{23}_D$ +109° (0.5 g/100 mL, $CHCl_3$); NMR (500 MHz) δ 4.15 and 4.08 (dd, 2, $COCH_2$, J_{gem} = 16.6 Hz), 4.84 (d, 1, H_{10},

(17) Hydrolysis of aryloxiranes is known to afford cis and trans stereoisomeric diols, the ratio of which is dependent upon pH and salt concentration. At low and intermediate pHs mixtures of cis and trans diols are produced, while at high pH only trans diols are usually formed, except in the presence of $LiClO_4$. Since relatively few examples have been investigated thoroughly, caution should be exercised in assigning the stereochemistry of unknown diol products. Rogers, D. B.; Bruice, T. C. *J. Am. Chem. Soc.* **1979**, *101*, 4713. Imuta, M.; Ziffer, J. H. *Ibid.* **1979**, *101*, 3990. Battistini, C.; Crotti, P.; Ferretti, M.; Macchia, F. *J. Org. Chem.* **1977**, *42*, 4067.

(18) Geacintov, N. E.; Gagliano, A. G.; Ibanez, V.; Lee, H.; Jacobs, S. A.; Harvey, R. G. *Biomol. Stereodynamics*, in press.

(19) Geacintov, N. E.; Ibanez, V.; Jacobs, S. A.; Harvey, R. G., submitted for publication.

(20) Wood, A. W.; Levin, W.; Thakker, D. R.; Yagi, H.; Chang, R. L.; Ryan, D. E.; Thomas, P. E.; Dansette, P. M.; Whittaker, N.; Turujman, S.; Lehr, R. E.; Kumar, S.; Jerina, D. M.; Conney, A. H. *J. Biol. Chem.* **1979**, *254*, 4408.

(21) Chang, R. L.; Levin, W.; Wood, A. W.; Lehr, R. E.; Kumar, S.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1981**, *41*, 915.

(22) Buening, M. K.; Levin, W.; Wood, A. W.; Chang, R. L.; Lehr, R. E.; Taylor, C. W.; Yagi, H.; Jerina, D. M.; Conney, A. H. *Cancer Res.* **1980**, *40*, 203.

(23) Holmes, D. F.; Adams, R. *J. Am. Chem. Soc.* **1934**, *56*, 2093.

(24) Harvey, R. G.; Lee, H. M.; Shyamasundar, N. *J. Org. Chem.* **1979**, *44*, 78.

$J_{10,11}$ = 3.0 Hz), 7.00 (s, 1, H_9), 7.87–8.43 (m, 8, Ar).

(+)-(9*R*,10*S*)-9,10-Epoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene ((+)-BePE). A solution of (−)-**1b** (54 mg, 0.1 mmol) and NaOMe (16 mg) in methanol (3 mL) and THF (3 mL) was stirred at room temperature under N_2 for 2.5 h. The product was partitioned between ether and water, and the ether layer was dried and evaporated. Trituration of the residue with cold ether–hexane (1:1) afforded (+)-BePE (20 mg, 74%) as a white solid: mp 132–133 °C; $[\alpha]^{23}_D$ +332.2° (0.475 g/100 mL, $CHCl_3$); NMR (500 MHz) δ 2.02 (m, 1, H_{11}), 2.70 (m, 1, H_{11}), 3.00 (m, 1, H_{12}), 3.58 (dd, 1, H_{12}), 3.93 (s, 1, H_{10}), 4.90 (d, 1, H_9, $J_{9,10}$ = 4.4 Hz), 7.98–8.05 (m, 4, $H_{2,4,5,7}$), 8.16 (d, 2, $H_{3,6}$, $J_{2,3}$ = $J_{6,7}$ = 7.5 Hz), 8.35 (d, 1, H_1, $J_{1,2}$ = 8.0 Hz), 8.61 (d, 1, H_8, $J_{7,8}$ = 8.0 Hz).

(−)-(9*S*,10*R*)-9,10-Epoxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene ((−)-BePE). Analogous reaction of (+)-**1b** furnished (−)-BePE: $[\alpha]^{23}_D$ −330.2° (0.525 g/100 mL, $CHCl_3$); the NMR spectrum of (−)-BePE was superimposable on that of (+)-BePE.

(+)-(9*S*,10*S*)-*trans*-10-Bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene ((+)-1a). A mixture of (+)-**1b** (84 mg, 0.15 mmol) and $LiAlH_4$ (6 mg) in anhydrous ether (10 mL) was stirred at room temperature for 30 min under anhydrous conditions. The reaction mixture was decomposed by addition of dilute acetic acid, and the ether phase was washed with water, dried, and evaporated to yield an oil. Crystallization from EtOAc gave (+)-**1a** (53 mg, 99%) as a white solid: $[\alpha]^{23}_D$ +10.6° (0.625 g/100 mL, THF); the NMR spectrum of (+)-**1a** was identical with that of the racemic **1a**.

(−)-(9*R*,10*R*)-*trans*-10-Bromo-9-hydroxy-9,10,11,12-tetrahydrobenzo[*e*]pyrene ((−)-1a). Analogous reaction of (−)-**1b** furnished (−)-**1a**: $[\alpha]^{23}_D$ −10.0° (0.54 g/100 mL, THF); the NMR spectrum of (−)-**1a** matched that of the racemic **1a**.

***trans*-10-Bromo-9-(*p*-methoxybenzoyloxy)-9,10,11,12-tetrahydrobenzo[*e*]pyrene (1c).** A solution of (+)-**1a** (10 mg, 0.028 mmol) and excess *p*-methoxybenzoyl chloride in pyridine (0.2 ml) was left at room temperature overnight. After the usual workup, trituration of the solid residue with cold ether gave 12.6 mg of white solid. Preparative TLC of the ether phase on silica gel eluted with benzene gave another 1 mg of product, affording a total of 13.6 mg (99%) of **1c**: mp 166–167 °C; NMR δ 2.6 (m, 2, H_{11}), 3.7 (m, 2, H_{12}), 3.8 (s, 3, OCH_3), 5.0 (m, 1, H_{10}), 6.8–7.3 (m, 4, Ar), 7.8–8.6 (m, 9, Ar). The CD spectrum of this diastereomer of **1c** (Figure 1) exhibited a negative first Cotton effect at 277 nm and a positive second Cotton effect at 254 nm, allowing assignment of its configuration as 9*S*,10*S*.

Similar treatment of (−)-**1a** gave the other enantiomer of **1c** the CD spectrum of which was a mirror image of the first, confirming its absolute configuration as 9*R*,10*R*.

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Registry No. (±)-**1a**, 88767-14-0; (+)-(9*S*,10*S*)-**1a**, 88824-51-5; (−)-(9*R*,10*R*)-**1a**, 88824-52-6; (+)-(9*S*,10*S*)-**1b**, 88824-53-7; (−)-(9*R*,10*R*)-**1b**, 88767-15-1; (9*S*,10*S*)-**1c**, 88780-81-8; (9*R*,10*R*)-**1c**, 88851-60-9; (+)-(9*R*,10*S*)-BePE, 88824-54-8; (−)-(9*S*,10*R*)-BePE, 88824-55-9; 9,10-dihydrobenzo[*e*]pyrene, 66788-01-0; (−)-menthoxyacetyl chloride, 15356-62-4; *p*-methoxybenzoyl chloride, 100-07-2.

Notes

Synthesis of Tetrathiafulvalene Doubly Fused to the 3,4-Position of Selenophene

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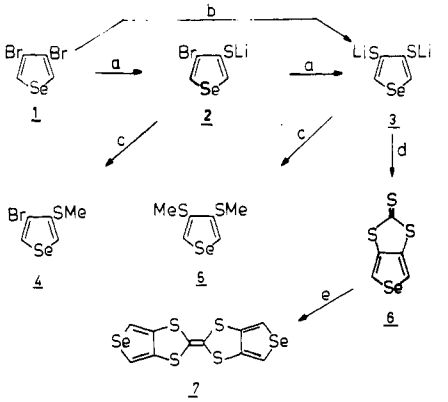
Tetrathiafulvalenes have received much attention in recent years as electron donors for preparation of electrical-conducting charge-transfer complexes.[1] Annelation of aromatic rings on the thiafulvalene system[2] and the use of selenium[3] and tellurium[4] analogues have provided interesting structural modifications. The goal of this work was to prepare the tetrathiafulvalene fused on both rings to the 3,4-position of selenophene.

Scheme I



(a) 1 BuLi; S_8 · (b) 2 BuLi; S_8 ·

(c) excess CH_3I · (d) $CSCl_2$ · (e) $P(OMe)_3$

Since the most general method for preparation of such tetrathiafulvalenes involves coupling of an appropriately substituted thione[5] or selenone,[6] our first synthetic goal

(1) (a) Narita, M.; Pittman, C. U., Jr. Synthesis **1976**, 489. (b) Engler, E. M.; Patel, V. V.; Andersen, J. R.; Schumaker, R. R.; Fukushima, A. A. *J. Am. Chem. Soc.* **1978**, *100*, 3769. (c) Cowan, D. O.; Kini, A.; Chiang, L.-Y.; Lerstrup, K.; Talham, D. R.; Poehler, T. O.; Bloch, A. N. *Mol. Cryst. Liq. Cryst.* **1982**, *86*, 1741/1.

(2) (a) Nakayama, J. *Synthesis* **1975**, 168. (b) Lerstrup, K.; Lee, M.; Wiygul, F. M.; Kistenmacher, T.; Cowan, D. O. *J. Chem. Soc., Chem. Commun.* **1983**, 294. (c) Johannsen, I.; Bechgaard, K.; Mortensen, K.; Jacobsen, C. *Ibid.* **1983**, 295.

(3) (a) Chiang, L.-Y.; Cowan, D. O.; Poehler, T. O.; Bloch, A. N. *Mol. Cryst. Liq. Cryst.* **1982**, *86*, 1767/27. (b) Bechgaard, K.; Cowan, D. O.; Bloch, A. N. *J. Chem. Soc., Chem. Commun.* **1974**, 937. (c) Fanghänel, E.; Schukat, G.; Schützenübel, J. *Z. Chem.* **1981**, *21*, 447. (d) Engler, E. M.; Green, D. C. *J. Chem. Soc., Chem. Commun.* **1976**, 148.

(4) Wudl, F.; Aharon-Shalom, E. *J. Am. Chem. Soc.* **1982**, *104*, 1154.

(5) Miles, M. G.; Wager, J. S.; Wilson, J. D.; Siedle, A. R. *J. Org. Chem.* **1975**, *40*, 2577. (b) Hünig, S.; Kiesslich, G.; Quast, H.; Scheutzow, D. *Liebigs Ann. Chem.* **1973**, 310. (c) Scherowsky, G.; Weiland, J. *Chem. Ber.* **1974**, *107*, 3155. (d) Le Coustumer, G.; Mollier, Y. *J. Chem. Soc., Chem. Commun.* **1980**, 38.

0022-3263/84/1949-1117$01.50/0