Tetrahedron Letters,Vol.24,No.45,pp 4903-4906,1983 0040-4039/83 $3.00 + .00
Printed in Great Britain

FACILE SYNTHESIS OF K-REGION ARENE OXIDES

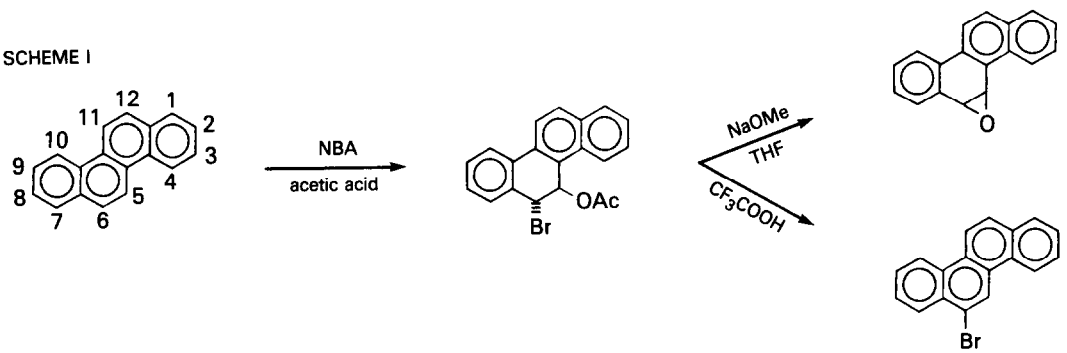
P. J. van Bladeren and D. M. Jerina*
Laboratory of Bioorganic Chemistry, NIADDK, National Institutes of Health, Bethesda, MD 20205

Summary: Polycyclic aromatic hydrocarbons react at the K-region with N-bromoacetamide in acetic acid to provide trans-bromohydrin acetates which are readily cyclized to arene oxides. The simplicity of the approach makes radioactive and optically active K-region arene oxides easily available.

K-Region arene oxides are of considerable chemical and biochemical interest[1]. In addition to their solvolytic and photochemical reactions, they are often major metabolites of the polycyclic aromatic hydrocarbons and can be highly mutagenic[1]. They are very useful substrates for the study of the mechanism of action of epoxide hydrolase[2] and the glutathione S-transferases[3]. A number of syntheses of K-region arene oxides have been described. These include i) ring-closure of 2,2'-biphenyldialdehydes with tris-dimethylaminophosphine[4], ii) conversion of cis-dihydrodiols *via* 1,3-dioxolanes to trans-chlorohydrin acetates which are then cyclized with base[5], iii) cyclization of trans-dihydrodiols with various reagents[6,7] and iv) direct oxidation with peracids or hypochlorite[8,9]. Each of these procedures suffers various drawbacks and only procedure ii) has allowed the synthesis of optically active products[2,10].

Cognizant of the fact that modestly stable trans-dibromides are formed on addition of bromine to the K-region of certain hydrocarbons[11], we have examined the reaction of polycyclic hydrocarbons with N-bromoacetamide (NBA) in acetic acid (Scheme I) and have found that trans-bromohydrin acetates can be formed directly from the parent hydrocarbon in many cases (Table I). In

SCHEME I

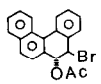
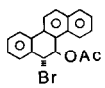
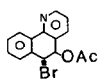


a typical reaction, a mixture of chrysene (250 mg) and NBA (1.2 eq.) was stirred in glacial acetic acid (75 mL) at rt for 1 day. Standard workup followed by facile preparative HPLC (α = 7) on a Du Pont Zorbax SIL column (21.2 x 250 mm eluted with 10% ethyl acetate in hexane, 1 injection) provided *trans*-5-acetoxy-6-bromo-5,6-dihydrochrysene (68%) and a mixture of chrysene and 6-bromochrysene[12]. Treatment of the 5,6-bromohydrin acetate with trifluoroacetic acid in chloroform at rt gave 6-bromochrysene[12], thus confirming the position of the 5-acetoxy and 6-bromo sub-

stituents as expected from simple electronic considerations and the reported position of bromination of chrysene[12]. The value of $J_{5,6}$ of the bromohydrin acetate (2.8 Hz) is consistent with the expected diaxial trans configuration. Attempts to consume all of the starting chrysene through the use of an even larger excess of NBA resulted in secondary bromination. A compound identified as *trans*-5-acetoxy-6-bromo-5,6-dihydro-12-bromochrysene[13] was formed in increasing amounts, presumably *via* 6-bromochrysene. Although this compound was not of interest in the present study, its formation indicates that certain brominated K-region arene oxides could be accessible by this methodology.

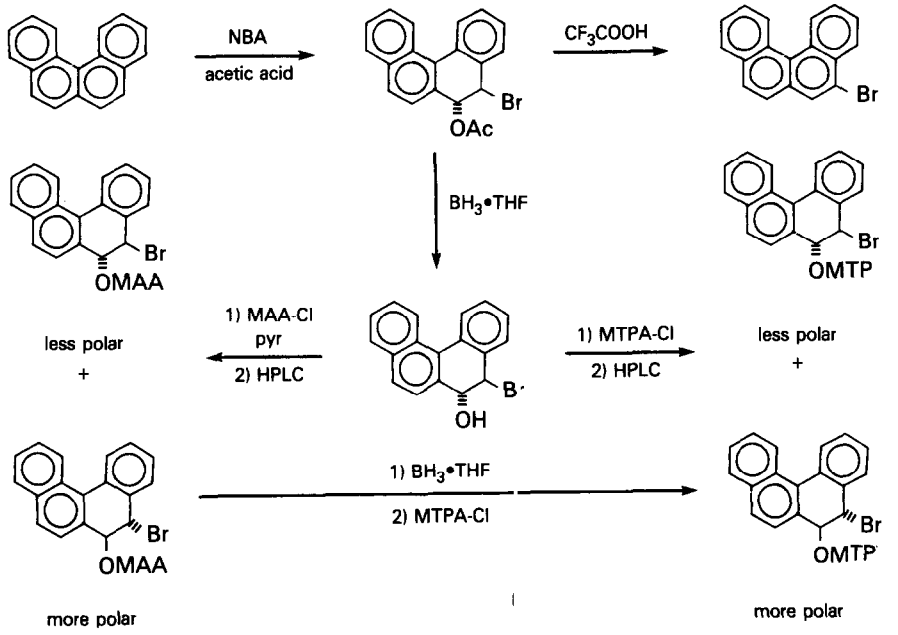
Several hydrocarbons were examined in order to determine the scope of the NBA reaction (Table I). In addition to chrysene, phenanthrene and benzo[c]phenanthrene were found to readily form bromohydrin acetates. In contrast, benz[a]anthracene and benzo[a]pyrene, both compounds with reactive L-regions, underwent bromination at the 7- and 6- positions, respectively. In an attempt to block a reactive L-region from reaction, 7,12-dimethylbenz[a]anthracene was examined, but only benzylic bromination was detected. Two azaphenanthrenes were examined. In both cases, reaction rates were somewhat retarded relative to phenanthrene (8% isolated yield of bromohydrin acetate for the 1-aza- and 39% for the 4-azaphenanthrene after 1 day) presumably due to protonation of nitrogen in the acetic acid. The pKa's of 1-aza- and 4-azaphenanthrene in water are 5.15 and 4.25, respectively[14]. However, the absence of detectable by-products suggests that high yields could be attainable with extended reaction times.

TABLE. Properties of K-region trans-bromohydrin acetates

Compound	Yield	m.p.	K-Region PMR Values (δ,TMS)[a]
	58%	72-74°C (Hexane)	5.41 6.17 J = 2.8 Hz[b]
	60%	132-136°C (ether/pet. ether)	5.36 6.18 J = 2.8 Hz[b]
	68%	135-140°C (EtOAc/hex)	5.52 7.05 J = 2.8 Hz[c]
 [d]	39%	128-131°C (EtOAc/hex)	5.61 6.18 J = 2.5 Hz[c]
 [d]	8%	140-143°C (EtOAc/hex)	5.49 6.25 J = 2.8 Hz[c]

a) Only the K-region doublets are given. Mass spectra for all compounds were in accord with their structures.
b) Spectrum taken in $CDCl_3$.
c) Spectrum taken in THF-d_8.
d) The proposed structures are based on the fact that the acetate substituent is expected at the carbon atom that best accomodates a positive charge.

SCHEME II



We have previously demonstrated that cyclization of halohydrin acetates with dry sodium methoxide in THF or ether provides a particularly clean and mild method for the generation of K-region[5] and non-K-region[15] arene oxides. To illustrate this point, the present bromohydrin acetates of phenanthrene and chrysene were stirred with dry sodium methoxide in THF (rt, 1 day), and the desired arene oxides [4,5,8,9] were isolated in >95% yield.

The present approach is amenable to the synthesis of optically active K-region arene oxides *via* prior resolution of the bromohydrins. To this end (Scheme II) *trans*-5-bromo-6-acetoxy-5,6-dihydrobenzo[c]phenanthrene was quantitatively converted to the free bromohydrin with diborane in THF[16,17] (rt, 16 hrs.) Extended reaction times resulted in displacement of the halogen substituent. The PMR spectrum in THF-d_8 + D_2O shows doublets for H_6 and H_5 at δ4.93 and δ5.36 with $J_{5,6}$ = 2.9 Hz. Treatment of the bromohydrin acetate with CF_3COOH in $CHCl_3$ (16 hrs, rt) provided 5-bromobenzo[c]phenanthrene (vide PMR, ref. 11) in confirmation of its structure. (-)-Menthoxyacetic acid (MAA) was examined as a resolving agent (α = 1.13 for the diastereomeric esters on a 21 x 250 mm Du Pont Zorbax SIL column eluted with 4% ether in cyclohexane). By analogy to earlier studies on the resolution of trans-bromohydrins as MAA ethers[16] we tentatively assign (5R, 6R) absolute configuration to the early-eluting diastereomer. The PMR spectrum (100 MHz,C_6D_6) shows a singlet for the $-OCH_2CO_2-$ signal at δ3.56 for this less polar isomer and a pair of doublets centered at δ3.48 and δ3.68 with J_{gem} = 16.5 Hz for the more polar diastereomer. The K-region signals are identical for both isomers and appear at δ5.22 and δ6.50 with $J_{5,6}$ = 2.9 Hz. The diastereomeric α-methoxy-α-trifluoromethyl-phenylacetic acid esters (MTPA) were more difficult to separate (α = 1.08, conditions as described for MAA esters). The more polar MAA ester and the more polar MTPA ester had identical configurations for their bromohydrin fragments as es-

tablished by retention time on HPLC after interconversion of the ester groups. The PMR data ($CDCl_3$) for the MTPA diastereomers suggests the same absolute configurational assignments as did the PMR data for the MAA diastereomers. The signal for the proton on the bromine-bearing C_5 carbon atom is further downfield for the more polar (5S,6S) diastereomer: δ5.51 for the more polar compared with δ5.36 for the less polar (5R,6R) diastereomer[18]. The signals for H_6 appear at δ6.39 (more polar) and 6.32 (less polar) with $J_{5,6}$ = 2.9 Hz in both cases. Since this PMR approach to assignment of absolute configuration has previously only been applied to bromohydrin esters on tetrahydrobenzo-rings and not to K-regions, experiments are in progress which we hope will make the present assignments definitive.

REFERENCES AND NOTES

1. Boyd, D. R. and Jerina, D. M.: Arene Oxides and Oxepins, In "Small Ring Heterocycles," Hassner, A. (Ed.) Vol. 42 (Part 3), John Wiley & Sons, Inc., New York., in press.
2. Armstrong, R. N., Kedzierski, B., Levin W. and Jerina, D. M., J. Biol. Chem. 256, 4726 (1981).
3. Cobb, D., Boehlert, C., Lewis, D. and Armstrong, R. N., Biochem. 22, 805 (1983).
4. Newman, M. S. and Blum, S. J. Am. Chem. Soc. 86, 5598 (1964).
5. Dansette, P. and Jerina, D. M., J. Am. Chem. Soc. 96, 1224, (1974).
6. Goh, S. M. and Harvey, R. G., J. Am. Chem. Soc. 95, 242 (1973).
7. Okamoto, T., Shudo, K., Kitahara, Y., and Nagata, N. Chem. Pharm. Bull. (Japan) 26, 2014 (1978).
8. Ishikawa, K. Charles, H. C., and Griffin, G. W., Tetrahedron Lett., 427 (1977).
9. Krishnan, S., Kuhn, D. G., and Hamilton, G. A., J. Am. Chem. Soc. 99, 8121 (1977).
10. a) Chang, R. L., Wood, A. W., Levin, W., Mah, H. D., Thakker, D. R., Jerina, D. M., and Conney, A. H. Proc. Natl. Acad. Sci. U.S.A. 76, 4280, (1979). b) Boyd, D. R., Gadaginamath, G. S., Sharma, N. D., Drake, A. F., Mason, S. F., and Jerina, D. M. J. Chem. Soc. Perkin I, 2223, (1980).
11. Ittah, Y., Thakker, D. R., Levin, W., Croisy-Delcy, M., Ryan, D. E., Thomas, P. E., Conney, A. H., and Jerina, D. M. Chem. Biol. Interact., in press and van der Linde, J., and Havinga, E., Rec. Trav. Chim. 84, 1047 (1965).
12. 6-Bromochrysene can also be obtained by treatment of chrysene with Br_2 (E. Clar "Polycyclic Hydrocarbons", Vol. I, Academic Press, London/N.Y., 1964, p. 251). Its PMR spectrum shows a characteristic 1H singlet at δ8.94 for the H_5 proton. The large downfield shift is due to both the bay-region and the proximate bromine substituent.
13. PMR ($CDCl_3$,TMS) doublets at 5.49 and 7.02 with $J_{5,6}$ = 2.8 Hz. M.S. (C.I., NO/N_2) 364-366 (M^+-HBr).
14. Albert, A., Goldacre, R., and Phillips, J. J. Chem. Soc. 2240 (1943).
15. Yagi, H., and Jerina, D. M. J. Am. Chem. Soc, 97, 3185 (1975).
16. Akhtar, M. H., Boyd, D. R., and Hamilton, G. A. J. Chem. Soc. Perkin I, 2437 (1979).
17. Although trans-halohydrins at the K-regions of the PAH are generally unknown, Kitahara et al. (Kitahara, Y., Shudo, K., and Okamoto, T. Heterocycles 8, 363 (1977)) have reported that 5-hydroxybenzo[f]quinoline reacts with 36% hydrochloric acid to form a cis-chlorohydrin and Lasne et al. (Lasne, M., Masson, S. and Thuillier, A. Bull. Soc. Chim. France, 1751 (1973)) have reported the trans-chlorohydrin of phenanthrene.
18. Balani, S. K., Boyd, D. R., Cassidy, E. S., Greene, R. M. E., McCombe, K. M., Sharma, N. D., and Jennings, W. B. Tetrahedron Lett. 22, 3277 (1981).

(Received in USA 25 July 1983)