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TETRAHYDROEPOXIDES AND DIOL EPOXIDES OF BENZ[C]ACRIDINE

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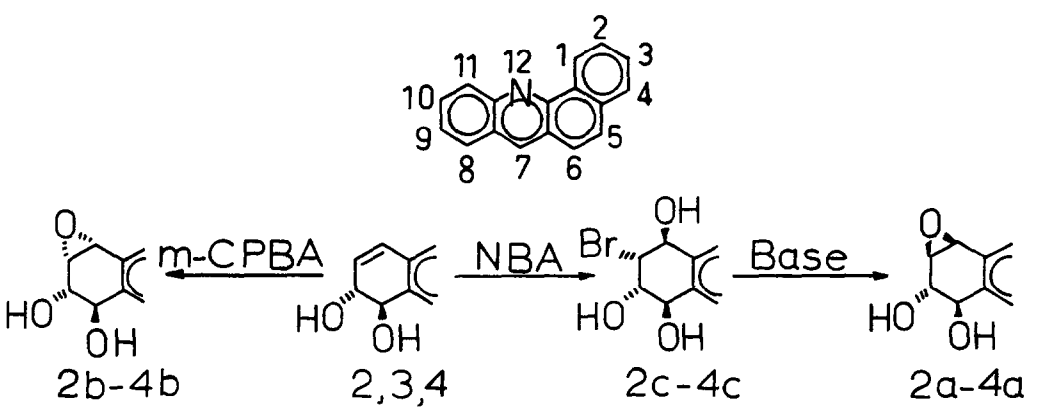
Abstract: The chemical synthesis and NMR characterization of the benzo ring tetrahydro- and diol epoxides of the carcinogen benz[c]acridine are described.

Chemical synthesis of the various positional and diastereomeric diol epoxides of selected polycyclic aromatic hydrocarbons (PAH) for biological studies has been an essential factor in establishing bay region diol epoxides as major contributors to PAH carcinogenicity.[1] Much less studied and understood is the basis for the carcinogenicity of aza-PAH, although tumor studies of benzacridines have revealed substituent effects similar to those for PAH.[2] For aza-PAH, only the bay region diol epoxides of benz[c]acridine[3,4] and the trans-bay region diol epoxide of benz[a]acridine have been reported.[4] We report herein the preparation and spectral properties of seven of the eight benzo ring diol epoxides of benz[c]acridine, and of the four benzo ring tetrahydroepoxides of benz[c]acridine. The latter molecules have proven to be effective probes of electronic and other effects in the mutagenesis of PAH.[5]

Generally, the diol epoxides have been accessible from dihydrodiols through methodology used for analogous PAH[6] (Scheme 1). Thus, treatment of the appropriate dihydrodiols (**2-4**) with a ten-fold excess of m-chloroperoxybenzoic acid for 1-2 hr. in dry THF under Ar gave the

SCHEME 1

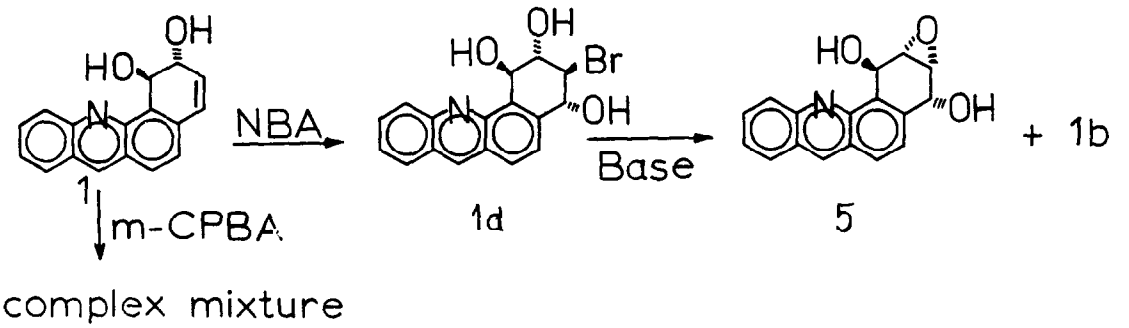


Partial structures for: 3,4-dihydro-3,4-dihydroxybenz[c]acridine, **2**; 8,9-dihydro-8,9-dihydroxybenz[c]acridine, **3**; 10,11-dihydro-10,11-dihydroxybenz[c]acridine, **4**.

trans-diol epoxides, **2b–4b**, in 47, 71 and 72% yields, respectively. Similarly, bromotriols **2c–4c** were obtained in 90, 42 and 39% yields, respectively, under normal conditions[6], except that acceptable yields of **4c** were obtained only when $HClO_4$ was substituted for HCl as the acid catalyst. Cyclization of the bromotriols to epoxides **2a–4a** was achieved in 66,64 and 95%, respectively, using $KOBu^t$ in anh. THF.

Contrary to the stereospecific reactions observed with dihydrodiols **2–4**, **1** yielded a complex reaction mixture with m-CPBA from which no diol expoxide was isolated. Similarly, treatment (Scheme 2) of **1** with NBA yielded a complex mixture. However, bromotriol **1d** could be

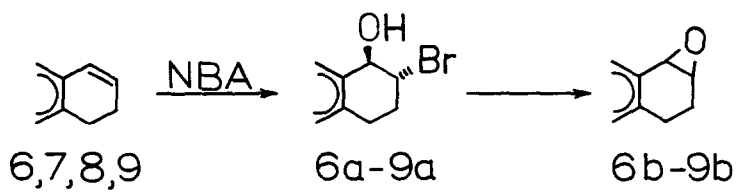
SCHEME 2



isolated from the mixture in 27% yield by dry column chromatography over silica gel using 40% EtOAc-hexane as developing solvent. Assignment of stereochemistry to **1d** is based upon its conversion to two diol epoxides, **1b** (38%) and **5**. The latter molecule was characterized as its diacetate derivative (Table) and exhibited expected[7] spectral properties. Thus, hopes that the unusual diequatorial conformation[3] of **1** in THF might lead to clean, stereospecific reactions were not realized.

The tetrahydroepoxides were prepared in all cases (Scheme 3) by cyclization of the corresponding bromohydrin. For the angular ring tetrahydroepoxides, **6b** and **7b**, attempted

SCHEME 3



Partial structures for: 3,4-dihydrobenz(c)acridine **6**; 1,2-dihydrobenz(c)acridine **7**; 10,11-dihydrobenz(c)acridine **8**; 8,9-dihydrobenz(c)acridine **9**.

TABLE. MELTING POINTS AND NMR SPECTRA OF BENZ[C]ACRIDINE BROMOTRIOLS, DIOL EPOXIDES AND TETRAHYDROEPOXIDES.

Compounds (MP)[d]	NMR SPECTRA[a,b,c]
2c (141-143)	4.3(H_3), 4.6(H_2), 4.7(H_4), 6.1(H_1), 7.4-8.8(6H), 9.0(H_7), $J_{1,2}$=4.4, $J_{2,3}$=2.2, $J_{3,4}$=7
3c (121-125)	4.4(H_{10}), 4.8(H_9), 5.0(H_{11}), 5.3(H_8), 7.6-8.1(5H), 8.5(H_7), 9.2-9.5(H_1), $J_{8,9}$=$J_{10,11}$=6.2, $J_{9,10}$=2.3
4c (155-157)	4.3(H_9), 4.7(H_{10}), 4.8(H_8), 5.0(H_{11}), 7.7-8.1(5H), 8.4(H_7), 9.1-9.4(H_1), $J_{8,9}$=4.7, $J_{9,10}$=1.9, $J_{10,11}$=8.5
1d (174-176)	4.6(H_2), 4.8(H_3), 5.2(H_4), 5.8(H_1), 7.5-8.3(6H), 9.0(H_7), $J_{1,2}$=4.7 $J_{2,3}$=2.3, $J_{3,4}$=6.7
2a (190-191)	3.9(H_2), 4.2(H_3), 4.7(H_4), 5.3(H_1), 7.5-8.3(6H), 9.1(H_7), $J_{1,2}$=4, $J_{3,4}$=2.5
3a (154-157)	3.9(H_{10}), 4.3(H_9), 4.4(H_{11}), 4.8(H_8), 7.6-8.2(5H), 8.4(H_7), 9.0-9.4(H_1), $J_{8,9}$=2, $J_{10,11}$=4
4a (189-192)	3.9(H_9), 4.4(H_8), 4.5(H_{10}), 4.8(H_{11}),7.6-8.2(5H), 8.6(H_7), 9.1-9.4(H_1), $J_{8,9}$=4, $J_{9,10}$=$J_{10,11}$=2
1b (187-190)	4.0(H_3), 4.3(H_4), 4.7(H_2), 6.2(H_1), 7.5-8.3(6H), 9.05(H_7), $J_{1,2}$=~1.0, $J_{3,4}$=4.0
2b (198-200)	3.8(H_2), 3.9(H_3), 4.6(H_4), 5.6(H_1), 7.5-8.4(6H), 9.1(H_7), $J_{1,2}$=4, $J_{2,3}$=0, $J_{3,4}$=8
3b (192-196)	3.8(H_{10}), 3.9(H_9), 4.4(H_{11}), 4.6(H_8), 7.6-8.2(5H), 8.5(H_7), 9.1-9.4(H_1), $J_{8,9}$=8, $J_{9,10}$=0, $J_{10,11}$=4.5
4b (141-144)	3.8(H_9), 4.0(H_{10}), 4.3(H_8), 4.6(H_{11}), 7.7-8.2(5H), 8.6(H_7), 9.3-9.5(H_1), $J_{8,9}$=4.5, $J_{9,10}$=0, $J_{10,11}$=4.5
6b (129-130)	1.7-2.2(1H), 2.4-3.3(3H), 4.0(H_2), 5.7(H_1), 7.2-8.3(6H), 8.7(H_7), $J_{1,2}$=~4
7b (136-137)	1.5-2.2(1H), 2.4-3.1(2H), 3.9(H_3), 4.0(H_4), 4.1-4.6(1H), 7.4-8.4(6H), 8.7(H_7), $J_{3,4}$=~4
8b (109-111)	1.7-2.2(1H), 2.4-2.9(1H), 3.0-3.3(2H), 3.9(H_9), 4.1(H_8), 7.5-8.0(5H), 8.2(H_7), 9.1-9.4(H_1), $J_{8,9}$=4.4
9b (112-114)	1.7-2.1(1H), 2.3-3.3(3H), 3.9(H_{10}), 4.4(H_{11}), 7.5-8.0(6H), 9.2-9.5(H_1), $J_{10,11}$=3.8
5-diacetate	2.1(3H), 2.2(3H), 3.7(1H), 3.9(1H), 6.6(H_4), 7.3-8.3(7H), 8.7(H_7), $J_{1,2}$=$J_{2,3}$=$J_{3,4}$=~1-2

[a]Reported in delta units with TMS as internal standard, J values in Hz [b]Spectra for 2c, 4c, 2a, 3a, 4a, 2b, 3b and 4b obtained in d_6-DMSO - CD_3OD; for 1b, 1d and 3c in d_6-acetone - CD_3OD; for 6b, 7b, 8b, 9b and 5-diacetate in $CDCl_3$ [c]Spectra for 1b, 1d, 6b-9b and 5-diacetate were recorded at 80 MHz, all others at 100 MHz [d]All melting points are uncorrected, all diol epoxides and tetrahydroepoxides gave correct exact masses for parent ions.

epoxidation of **6** and **7** with m-CPBA led to complex mixtures, in contrast to the clean reaction of the corresponding dihydrodiol, **2**. Cleavage of the central acridine ring, as observed for 1,2,3,4-tetrahydrobenz[c]acridine[3], may be occurring, but product identification was not pursued. Epoxides **7b–9b** were obtained in 45, 11 and 23% yields from their respective alkene, **7–9**, upon cyclization of the intermediate bromohydrin with $KOBu^t$ in THF. For bromohydrin **6a**, attempted cyclization with $KOBu^t$ was unsuccessful, but conversion to the bay region epoxide, **6b**, was achieved in 96% yield using Amberlite (^-OH form)in anh. THF[6] (overall yield from the alkene; 25%).

In the NMR spectra, the most conspicuous feature occurs in the compounds substituted in the angular benzo ring. In all such cases, the absorption at lowest field is for the meso hydrogen, H_7, which appears as a singlet between 8.7 and 9.1 delta units. For compounds substituted in the non-angular benzo ring the lowest field absorption is for the bay region hydrogen atom, H_1, which appears as a multiplet between 9.0 and 9.5 delta units.

Of the epoxides, only bay region epoxides 2a,2b and 6b are highly mutagenic toward mammalian and bacterial cells.[7] Tumor studies are in progress.

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