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N-OXIDATION VERSUS EPOXIDATION IN POLYCYCLIC AZAARENES

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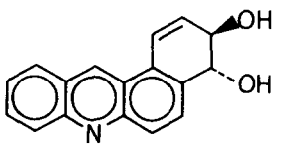
Abstract: Oxidation of the 3,4-dihydrodiols of benzacridines yielded preferably N-oxides in the [a]series and in the [c]series the bay region epoxide thus suggesting different metabolic pathways for noncarcinogenic and carcinogenic azaarenes.

Since a long time it is known that the substituted benz[c]acridines are more carcinogenic than the corresponding substituted benz[a]acridines[1]. In contrast to noncarcinogenic 12-methylbenz[a]acridine 7-methylbenz[c]acridine was found to exhibit strong carcinogenic activity[1,2]. Recently we synthesized the 3,4-dihydrodiols 1 and 2 of the parent heterocycles[3] which were chosen as model systems to elucidate the oxidative metabolism of polycyclic azaarenes (PAA) with regard to the biological difference of the [a] and [c] series. In analogy to polycyclic aromatic hydrocarbons (PAH) 1 and 2 are supposed to be proximate carcinogenic metabolites of PAA.



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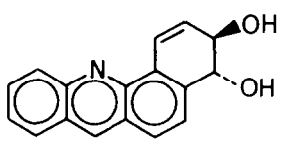

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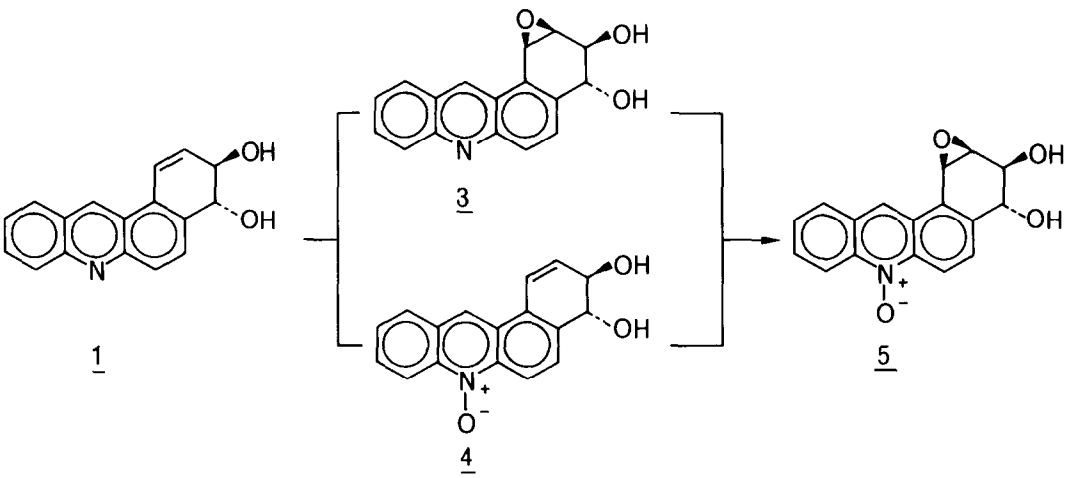
Mutagenicity (Ames) tests of 1 and 2 indicate that after metabolic activation diol 1 is not mutagenic in contrast to diol 2[4]. The reason for this may be either that diol 1 is not metabolized in vivo to the corresponding epoxide (different metabolic pathways of 1 and 2) or that the diol epoxide is not mutagenic (different mutagenic activities of the epoxides of 1 and 2). To gain insight into these correlations we synthesized the bay region epoxides of 1 and 2.

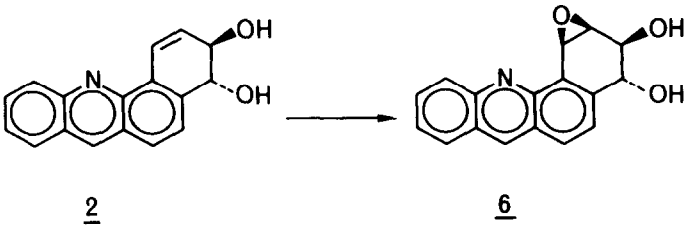
On reaction of 1 with a 10 molar excess of m-chloroperbenzoic acid in dry THF 3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-teterahydrobenz[a]acridine 7 oxide 5 was formed in 69 % yield as a yellow fluorescent solid of dec. point 185°C. The N-oxide structure of the product was deduced from the mass spectrum (M^+ = m/e 295) and the ^{1}H-NMR data (table 1), i. e. the high field resonance of the

meso proton H-12 as compared with starting material[3]. If we added only equimolar amounts of peracid two other reaction products were obtained together with 5. After chromatography on silica gel with ethyl acetate/THF a yellow solid decomposing at 115°C was isolated in 40 % yield representing the bay region epoxide of 1 (3). The third product was trans-3,4-dihydroxy-3,4-dihydrobenz[a]acridine 7-oxide 4, isolated in 23 % yield, a dark yellow solid decomposing at 105°C. 3 and 4 could be oxidized further to epoxy N-oxide 5.



The cis configuration of the epoxide ring with regard to the neighbouring hydroxy group is shown in the ^{1}H-NMR spectra of 3 and 5 by the coupling constant $I_{2,3} \simeq 1$ Hz (I_{trans} should be < 2.5 Hz[5]) and is due to the directing influence of the allylic hydroxy function[6]. The chemical shifts of protons H-1.. H-4 (table 1) in compunds 3 and 5 are consistent with the data reported for the 3,4-diol-1,2-epoxide of benz[a]anthracene[7]. That 4 represents the N-oxide of 1 can be seen from the resonance of H-12 at higher field as compared to the chemical shift of H-12 in diol 1 ($\Delta\delta$ = 0.6 ppm)[3].

A completely different oxidation pattern was found for the dihydrodiol 2 of benz[c]acridine. On reaction with a 10 molar excess of m-chloroperbenzoic acid under the same conditions as described for 1 dihydrodiol 2 exclusively formed the epoxide 6, a yellow solid decomposing above 169°C, in 72 % yield.



The structure of 6 is documented by its mass spectrum (M^+ = m/e 279) and the ^{1}H-NMR data (table 1). The aliphatic protons of diol epoxides 3, 5 and 6 exhibit similar chemical shifts except for H-1 the resonance of which is significantly shifted to lower field in compound 6 due to the anisotropy effect of the nitrogen atom in peri position to H-1.

Even with the strong oxidizing agent 3,5-dinitroperbenzoic acid[8] no N-oxide was obtained from 2. The resistance of 2 towards N-oxidation could have been suspected to result from a reduced electron density of the nitrogen in the [c]system although both 1 and 2 are acridine derivatives generally exhibiting enough basicity for N-oxidation[9]. To test this we determined the basicity constants of 1 and 2 by the UV spectroscopic method. pK values of 1 and 2 were found to be 5.19 ± 0.05 and 4.32 ± 0.05, respectively. From the fact that even weak basic heterocycles, e. g. 2-bromopyridine with a pK value of 0.9 can be N-oxidized with peracids[10] it seems rather improbable that the small difference between the basicities of 1 and 2 should account for the different oxidation pattern of 2. N-oxidation reactions are known to be sensitive to steric hindrance[11], as e. g. 2,6-diphenylpyridine yielded the N-oxide only in very low amount as compared to 2-phenylpyridine[12]. In the case of 8-methyl-2-phenylquinoline no oxidation product could be obtained at all[13]. Benz[a]phenazine was converted to the 7-oxide in good yield whereas further oxidation of the nitrogen in 12-position could be achieved only under drastic

Table 1: ^{1}H-NMR SPECTROSCOPIC DATA OF TRANS DIOL EPOXIDES (N-OXIDES) OF BENZ[A]- AND -[C]ACRIDINE[a)]

	H-1	H-2	H-3	H-4	H-7/12	H-5..11	$I_{1,2}$	$I_{2,3}$	$I_{3,4}$
trans-3,4-dihydroxy-3,4-dihydrobenz[a]-acridine 7-oxide 4	7.49	6.36	4.46	4.83	9.00	7.6-8.7	10.2	2.4	10.0
3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[a]-acridine 3	5.16	3.89	3.96	4.69	9.80	7.3-8.4	4.5	<1	8.4
3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[a]-acridine 7-oxide 5	5.09	3.85	3.95	4.53	9.30	7.6-8.9	4.8	<1	8.4
3α,4β-dihydroxy-1α,2α-epoxy-1,2,3,4-tetrahydrobenz[c]-acridine 6	5.70	4.10	4.03	4.77	9.10	7.5-8.4	4.6	<1	7.8

a) 90 MHz, chemical shifts in ppm (δ) with TMS as internal standard; coupling constants I in Hz; spectra were recorded in DMSO-d_6/D_2O.

conditions in very low yield[14]. In analogy we suppose steric hindrance by the angular ring peri to the nitrogen atom to be responsible for the inertness of 2 towards N-oxidation.

If we extend these findings on the oxidative metabolism of the parent heterocycles, benz[a]- and -[c]acridine, it seems plausible that benz[a]acridine should be metabolized predominantly to N-oxide derivatives whereas benz[c]acridine and PAA with bulky substituents peri to the nitrogen atom (i. e. nitrogen next to the bay region) are prohibited to form N-oxides in vivo. Formation of water soluble N-oxides in vivo could be an effective detoxification mechanism for PAA[15]. The main metabolic pathway of nicotine and several drugs with pyridine moiety proceeds via N-oxidation[16]. It is obvious that different metabolic pathways for the [a] and [c]series of azaarenes will result in different carcinogenic activities. To further test this hypothesis the diol epoxides 3 and 6 are subjected to mutagenicity studies at present[4].

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