SYNTHESIS AND SOME REACTIONS OF BENZO[f]QUINOLINE-5,6-OXIDE

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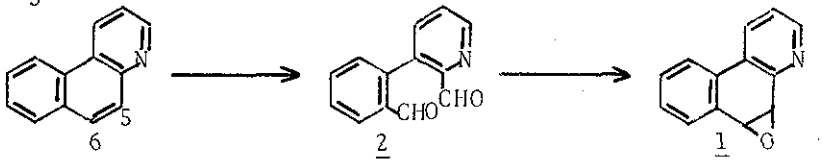
Benzo[f]quinoline-5,6-oxide, a possible active metabolite of benzo[f]quinoline, was prepared and the chemical reactions of the oxide were examined.

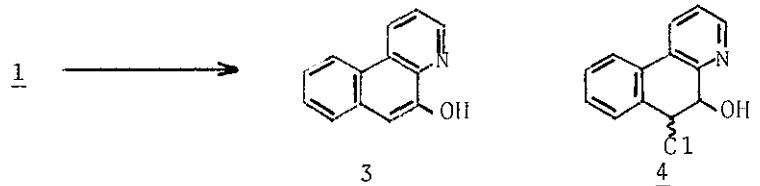
The importance of arene oxides as primary intermediates in oxidative metabolism of polynuclear aromatic hydrocarbons has been established.[1] In the present paper,we describe the synthesis and fundamental reactions of benzo[f]quinoline-5,6-oxide(1), a possible active metabolite of benzo[f]quinoline which has been isolated from soybean tar and is weakly mutagenic in bacteria.[2]

Oxidation of benzo[f]quinoline with ozone in methanol at -30--50° gave a dialdehyde(2, mp 79.5-81°) in 62% yield.[3,4] Oxirane ring formation from the dialdehyde with the use of tris(dimethylamino)phosphine gave benzo[f]quinoline-5,6-oxide(1),mp 161-161.5°, nmr($CDCl_3$,δ);4.59(d, J=3 Hz) and 4.75(d, J=3 Hz), in 65% yield.



As reactions of the epoxide(1), an acid catalyzed isomerization to phenol, nucleophilic additions of hydroxide and methoxide, and a photochemical reaction were examined.

The acid catalyzed isomerization of 1 with trifluoroacetic acid in dichloromethane or 24% hydrobromic acid gave quantitatively 5-hydroxybenzo[f]quinoline(3, mp 105-106°). The assignment of the structure(3) was confirmed by the formation of copper chelate, $(C_{13}H_8NO)_2Cu$ (mp >300°) with the use of copper sulfate solution. The same phenol was obtained by heating the crystalline epoxide at 200° (stable at 120°).

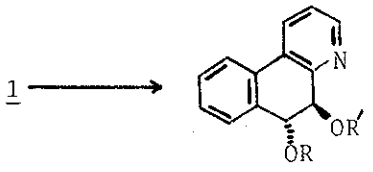


3 4

The reaction of 1 with 36% hydrochloric acid is interesting. The major product isolated(55%) was a hydroxy chloride(4, mp 208-210°). The phenol was also isolated as the minor product(14%). Since heating a solution of 4 in pyridine (100°) gave 5-hydroxybenzo[f]quinoline(3) in a good yield, the position of the hydroxy group is C-5. The configulation of the hydroxy group and chlorine atom is not established, though nmr coupling constant (2Hz, in C_5D_5N) of two hydrogens at C-5 and C-6 positions suggests cis configulation. 6-Chlorobenzo[f]quinoline(mp 79-80°) was obtained from the methanesulfonate(mp 151.5-152°) of the hydroxy chloride by heating in pyridine. The formation of a hydroxy chloride has not been known in the chemistry of carbocyclic arene oxides.

Another basic reaction of arene oxides is the formation of

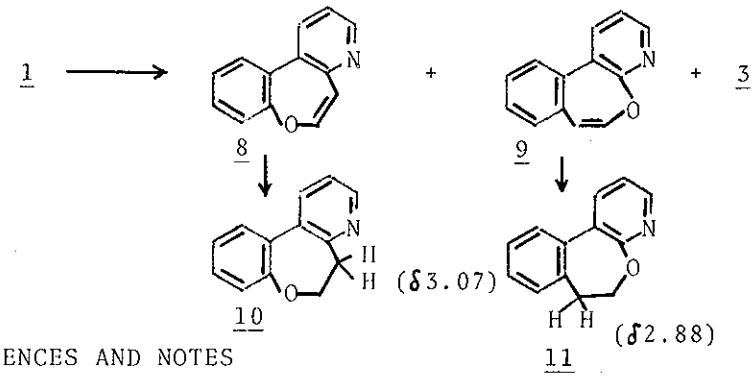
dihydroxy compounds, which is metabolically important. When 1 was heated at 75° in 5% sodium hydroxide for 4 hr, 5,6-dihydroxy-5,6-dihydrobenzo[f]quinoline(5,mp 237-240°) was obtained in 70% yield. The configulation of two hydroxy groups is clearly trans($J_{5,6}$=11 Hz in $CDCl_3$).In order to know the regioselectivity of the attack of a nucleophile, we studied the nucleophilic addition of methoxide in methanol. The reaction gave two methoxy alcohols, and trans-5-hydroxy-6-methoxy-5,6-dihydrobenzo[f]quinoline(6,mp 177-178°,46%) and trans-5-methoxy-6-hydroxy-5,6-dihydrobenzo[f]quinoline(7, mp 178-179.5°,22%) were isolated. The stereochemistry of hydroxy and methoxy groups at 6 is trans from the coupling constant (10 Hz in $CDCl_3$) of two hydrogens at C-5 and C-6 positions.[5] The stereochemistry of 7 may be also trans ($J_{5,6}$=7 Hz in $CDCl_3$).[5] Since the dehydration product of 7 with methanesulfonyl chloride was identical with the methyl ether(mp 95-96°) prepared from 3 with the use of diazomethane, the position of the methoxy group of 7 is C-5. Similary, 6 gave 6-methoxybenzo[f]quinoline (mp 94-95°). Since hydroxide is similar to methoxide, the regioselectivity of hydroxide attack on C-5 and C-6 may be also nearly 1:2.



5 R=H, R′=H
6 R=CH_3, R′=H
7 R=H, R′=CH_3

One of the most characteristic reactions of arene oxides is the isomerization to oxepins by UV irradiation.[6] When 1 was irradiated in dichloromethane with a low pressure mercury lamp, a mixture of oxepins was isolated in addition to 5-hydroxybenzo[f]quinoline(3,

6%)(but no 6-hydroxybenzo[f]quinoline). Separation of two isomers was achieved by silica gel thin layer chromatography with dichloromethane-hexane as eluent, and 8, mp 49-51°, nmr($CDCl_3$,δ);6.27(1H, d,J=6 Hz) and 6.82(1H,d,J=6 Hz)(12%) and 9, mp 110-111°, nmr($CDCl_3$, δ);6.14(1H,d,J=6 Hz) and 6.71(1H,d,J=6 Hz)(6%) were obtained. The oxepins 8 and 9 were catalytically reduced to dihydrooxepins (10 and 11, respectively) by the use of Pd-C catalyst. The more deshielded chemical shift(3.07δ) of $-\underline{CH_2}-CH_2-O-$ for 10 than that (2.88δ) for 11 suggests the structures shown, taking into consideration of the higher chemical shift of 2-ethylpyridine ($CH_3-\underline{CH_2}-$ 2.85δ) than that of ethylbenzene ($CH_3-\underline{CH_2}-$ 2.60δ).



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