

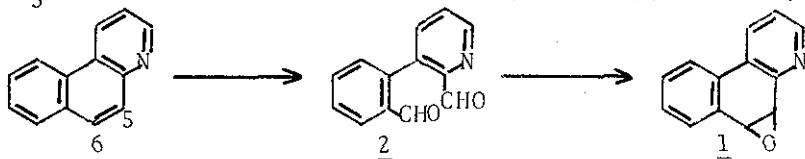
SYNTHESIS AND SOME REACTIONS OF BENZO[f]QUINOLINE-5,6-OXIDE

Yoshiyasu Kitahara, Koichi Shudo, and Toshihiko Okamoto*
Faculty of Pharmaceutical Sciences, University of Tokyo,
Hongo, Bunkyo-ku, Tokyo, Japan

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.

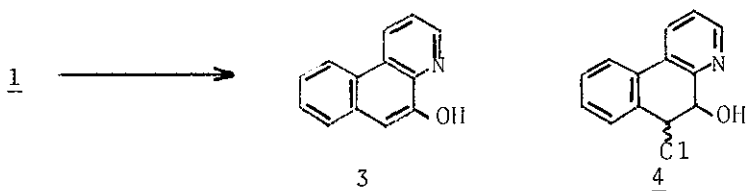
The importance of arene oxides as primary intermediates in oxidative metabolism of polynuclear aromatic hydrocarbons has been established.¹ In the present paper, we describe the synthesis and fundamental reactions of benzo[f]quinoline-5,6-oxide(1), a possible active metabolite of benzo[f]quinoline which 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(dimethyl-
 amino)phosphine gave benzo[f]quinoline-5,6-oxide(1), mp 161-161.5°,
 nmr(CDCl₃, 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.

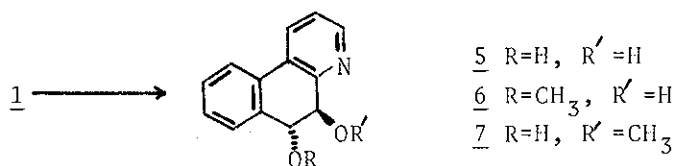
The acid catalyzed isomerization of 1 with trifluoroacetic acid in dichloromethane or 24% hydrobromic acid gave quantitatively 5-hydroxybenzo[f]quinoline(3, mp 105-106°). The assignment of the structure(3) was confirmed by the formation of copper chelate, $(C_{13}H_8NO)_2Cu$ (mp >300°) with the use of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



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 configuration 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 configuration. 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.

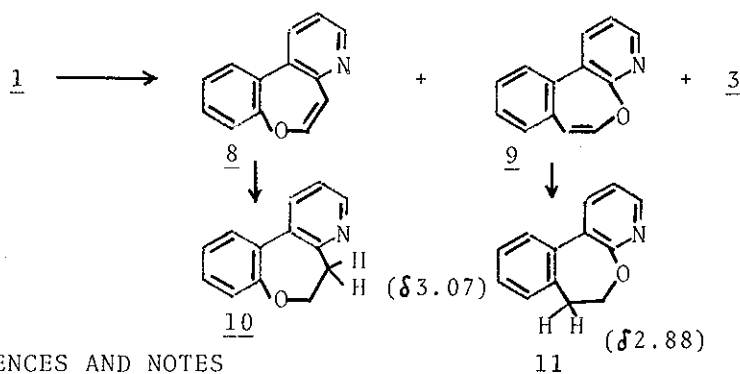
Another basic reaction of arene oxides is the formation of

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 configuration 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. Similarly, 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.



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(CDCl₃, δ); 6.27(1H, d, J=6 Hz) and 6.82(1H, d, J=6 Hz)(12%) and 9, mp 110-111°, nmr(CDCl₃, 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(3.07 δ) of -CH₂-CH₂-O- for 10 than that (2.88 δ) for 11 suggests the structures shown, taking into consideration of the higher chemical shift of 2-ethylpyridine (CH₃-CH₂- 2.85 δ) than that of ethylbenzene (CH₃-CH₂- 2.60 δ).



REFERENCES AND NOTES

- 1 J.W.Daly, D.M.Jerina, and B.Witkop, *Experientia*, 1972, 28, 1129
- 2 T.Kosuge and H.Zenda, *J.Syn.Org.Chem.(Japan)*, 1976, 34, 612
T.Kosuge, private communication.
- 3 P.S.Bailey and R.E.Erickson, *Org.Syn.*, 1961, 41, 41
- 4 All new compounds had satisfactory ir, nmr, and mass spectra and combustion analyses.
- 5 F.A.Beland and R.G.Harvey, *J.Amer.Chem.Soc.*, 1976, 98, 4963
- 6 K.Shudo and T.Okamoto, *Chem.Pharm.Bull.*, 1973, 21, 2809
N.E.Brightwell and G.W.Griffin, *J.Chem.Soc.Chem.Comm.*, 1973, 37

Received, 5th August, 1977