Tetrahedron Letters No. 33, pp 2811 - 2814, 1975. Pergamon Press. Printed in Great Britain.

METABOLITES OF POLYCYCLIC AROMATIC HYDROCARBONS. II. ISOMERIC K-REGION PHENOLS AND METHYL ETHERS OF BENZ[a]ANTHRACENE

J. G. Wiley, Jr.,* G. S. Menon, D. L. Fischer, and J. F. Engel
Midwest Research Institute, Kansas City, Missouri 64110

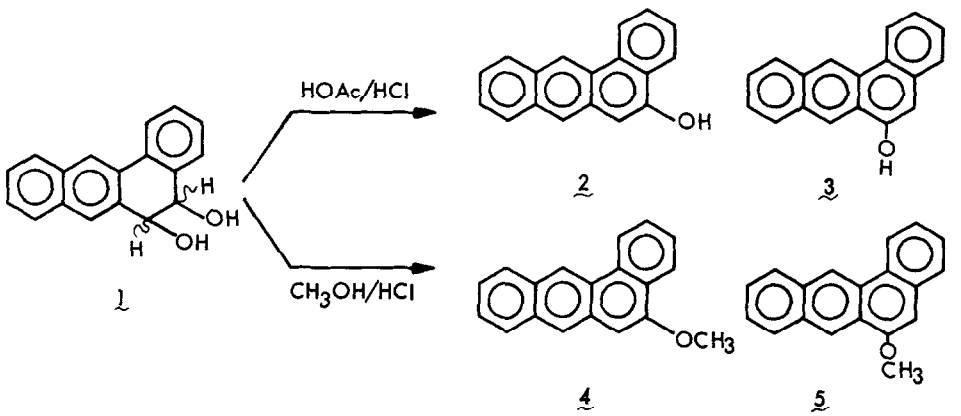
(Received in USA 25 March 1975; received in UK for publication 1 July 1975)

Polycyclic aromatic hydrocarbons (PAH) are metabolized primarily by enzymatic oxygenation which converts the hydrocarbons into polycyclic phenols, dihydrodiols, quinones, etc., and water-soluble conjugates.[1] These metabolites are thought to be formed via epoxide intermediates,[2] which readily isomerize to phenols. Metabolic studies of carcinogenic PAH require the availability of authentic samples of these metabolites, thus we have recently re-examined the syntheses of some PAH K-region phenols via acid-catalyzed dehydration of their parent cis-dihydrodiols.

The acid-catalyzed dehydration of PAH K-region dihydrodiols via a carbonium ion mechanism, in the absence of steric or electronic interactions from neighboring groups, should form both isomeric K-region phenols. Indeed, both isomeric K-region benzo[a]pyrenols have been reported.[3] However, benz[a]anthracene (BA), dibenz[a,h]anthracene (DBA), and 7,12-dimethylbenz-[a]anthracene (DMBA) have been reported[3] to form only one of the isomeric phenols on acid-catalyzed dehydration of their K-region dihydrodiols.

One K-region phenol of BA, 5-hydroxybenz[a]anthracene (2), and its methyl ether (4) were prepared by Fieser and Dietz[4] via an unequivocal route, and by a number of other investigators utilizing a variety of methods.[3,5,6] The other isomeric phenol, 6-hydroxybenz[a]anthracene (3), and its methyl ether were unknown.[7] We now report the preparation of both 2 and 3 by

acid-catalyzed dehydration of cis-5,6-dihydrobenz[a]anthracene-5,6-diol (1) utilizing the method of Cook and Schoental.[3] The corresponding methyl ethers 4 and 5 were also prepared by acid treatment of 1 in methanol.[8]



A crude mixture of 2 and 3 was formed by refluxing (1.5 hr) a solution of 1 in acetic acid containing a few drops of conc HCl. Addition of a few drops of water and cooling precipitated crude 2. Crystallization from toluene afforded 5-hydroxybenz[a]anthracene (2) as golden crystalline clusters,[9,10] mp 202-204° (lit.[6] mp 201-203°), yield 43%, ir (nujol) 3150 cm^{-1} (broad assoc. OH), nmr, DMSO-d_6, $(CH_3)_4Si$, δ7.17 (s, 1H, 6-H), δ8.20 (s, 1H, 7-H) and δ9.25 (s, 1H, 12-H); uv max (95% C_2H_5OH) 305 nm (log ε 4.48), 289 (4.63), 282 (4.71), 260 (4.54), and 255 (4.54). The isomeric 6-hydroxybenz[a]anthracene (3) was obtained as tan crystals by crystallization of the crude isomeric mixture from aqueous acetic acid, mp 139-140°, yield 33%, ir (nujol) 3330 cm^{-1} (assoc. OH), nmr, DMSO-d_6, $(CH_3)_4Si$, δ6.98 (s, 1H, 5-H), δ8.82 (s, 1H, 7-H) and δ9.33 (s, 1H, 12-H); uv max (95% C_2H_5OH) 301 nm (log ε 4.53), 289 (4.63), 278 (4.61), and 267 (4.64).

The methyl ethers 4 and 5 were prepared by refluxing (4 hr) the dihydrodiol 1 in methanol containing a few drops of conc HCl. Fractional crystallization from aqueous methanol afforded 5-methoxybenz[a]anthracene (4) as colorless crystals, mp 166-167° (lit.[4] mp 167-168°), nmr, CS_2, $(CH_3)_4Si$, δ3.92 (s, 3H, OCH_3), δ6.75 (s, 1H, 6-H), δ7.94 (s, 1H, 7-H) and δ8.80 (s,

1H, 12-H); uv max (95% C_2H_5OH) 301 nm (log ε 4.56), 286 (4.90), 280 (4.83), 259 (4.67), and 255 (4.66), gc 2 m x 2 mm column of 5% N,N'-bis(p-methoxybenzylidene)-α, α'-bis-p-toluidine (liquid crystal) on 120/140 mesh HMDS-treated chromosorb W at 250°, retention time 4.5 min. The isomer, 6-methoxybenz[a]anthracene (5), was then isolated from the mother liquor of 4 as long colorless needles, mp 115-116°, yield 30%, nmr, CS_2, $(CH_3)_4Si$, δ3.97 (s, 3H, OCH_3), δ6.62 (s, 1H, 5-H), δ8.62 (s, 1H, 7-H) and δ8.85 (s, 1H, 12-H); uv max (95% C_2H_5OH) 293 nm (log ε 4.64), 285 (4.72) 277 (4.70), and 265 (4.71), gc (same conditions as for 4), retention time 3.5 min.

We have demonstrated that both isomeric BA phenols, 2 and 3, and their methyl ethers, 4 and 5, are produced by acid treatment of BA dihydrodiol (1) and that the isolation of 3 provides a simple route to this new potential metabolite of BA. We might also expect that isomeric K-region phenols and methyl ethers of other PAH could be prepared by acid treatment of their parent dihydrodiols. Nmr studies have confirmed the formation of two isomeric DBA methyl ethers,[11] but that only 5-methoxy-7,12-dimethylbenz[a]anthracene is formed in the case of DMBA.[8] Separation and isolation of DBA methyl ethers and phenols are now in progress.

Acknowledgment. This investigation was supported by Contract No. NO1-CP-33387 from the National Cancer Institute.

References and Footnotes

(1) For leading references see J. K. Selkirk, R. G. Croy, and H. V. Gelboin, Sci., 184, 169 (1974).

(2) For comprehensive reviews of the role of arene oxides in metabolism see D. M. Jerina, ibid., 185, 573 (1974) and P. Sims and P. L. Grover in "Advances in Cancer Research," Vol. 20, G. L. Klein and S. Weinhouse, Eds., Academic Press, New York (1974).

(3) J. W. Cook and R. Schoental, J. Chem. Soc., 1948, 170.

(4) L. F. Fieser and E. M. Dietz, J. Am. Chem. Soc., 51, 3141 (1929).

(5) E. Boyland and P. Sims, Biochemical. J., 91, 493 (1964).

(6) M. S. Newman and J. Blum, J. Am. Chem. Soc., 86, 5598 (1964).

(7) 6-Hydroxybenz[a]anthracene has not been reported. The reference to it, Chem. Abstr., 39, 2126[2] (1945), is incorrect; the original reference, Tumori[2] 14, 273 (1940), actually refers to the 4-hydroxybenz[a]anthracene.

(8) In an attempt to prepare 5-hydroxy-7,12-dimethylbenz[a]anthracene by acid-catalyzed dehydration of the K-region dihydrodiol in refluxing methanol, 5-methoxy-7,12-dimethylbenz[a]anthracene (88%) was isolated instead. This method was then used to provide both methyl ethers 4 and 5. A recent publication, M. S. Newman and J. Blum, J. Am. Chem. Soc., 96, 6207 (1974), reports the synthesis of both K-region methyl ethers of DMBA from their acetates by a similar method.

(9) During crystallization of golden 5-hydroxybenz[a]anthracene (2) we noticed that two other colored forms of the phenol could be obtained, a dark green crystalline solid from acetic acid and a dull red crystalline solid from a dilute toluene solution. These colored forms had the same mp, spectra, and elemental analysis as golden 2. Neither form depressed the mp of 2 on admixture and thermal analysis revealed that these phenols were not solvated. TLC analyses of both colored forms of the phenol provided the same R_f values and revealed no impurities. The gold-colored form of the phenol 2 could be converted to either of the other forms by proper choice of solvent and concentration. We believe these colored phenols are different crystalline forms or intermolecular charge-transfer complexes of 2.

(10) All compounds gave C and H analyses and mass spectra data consistent with their structure.

(11) The nmr spectrum of the isomeric mixture of DBA methyl ethers in CS_2, $(CH_3)_4Si$; 5-methoxydibenz[a,h]anthracene, δ3.98 (s, 3H, OCH_3) and δ6.91 (s, 1H, 6-H); 6-methoxydibenz[a,h]anthracene, δ4.00 (s, 3H, OCH_3) and δ6.72 (s, 1H, 5-H).