Tetrahedron Letters No. 40, pp 3533 - 3536, 1977. Pergamon Press. Printed in Great Britain.

SYNTHESIS OF A BIOLOGICALLY ACTIVE D-RING DIOLEPOXIDE OF THE POTENT CARCINOGEN 7,12-DIMETHYLBENZ[a]ANTHRACENE (2)†

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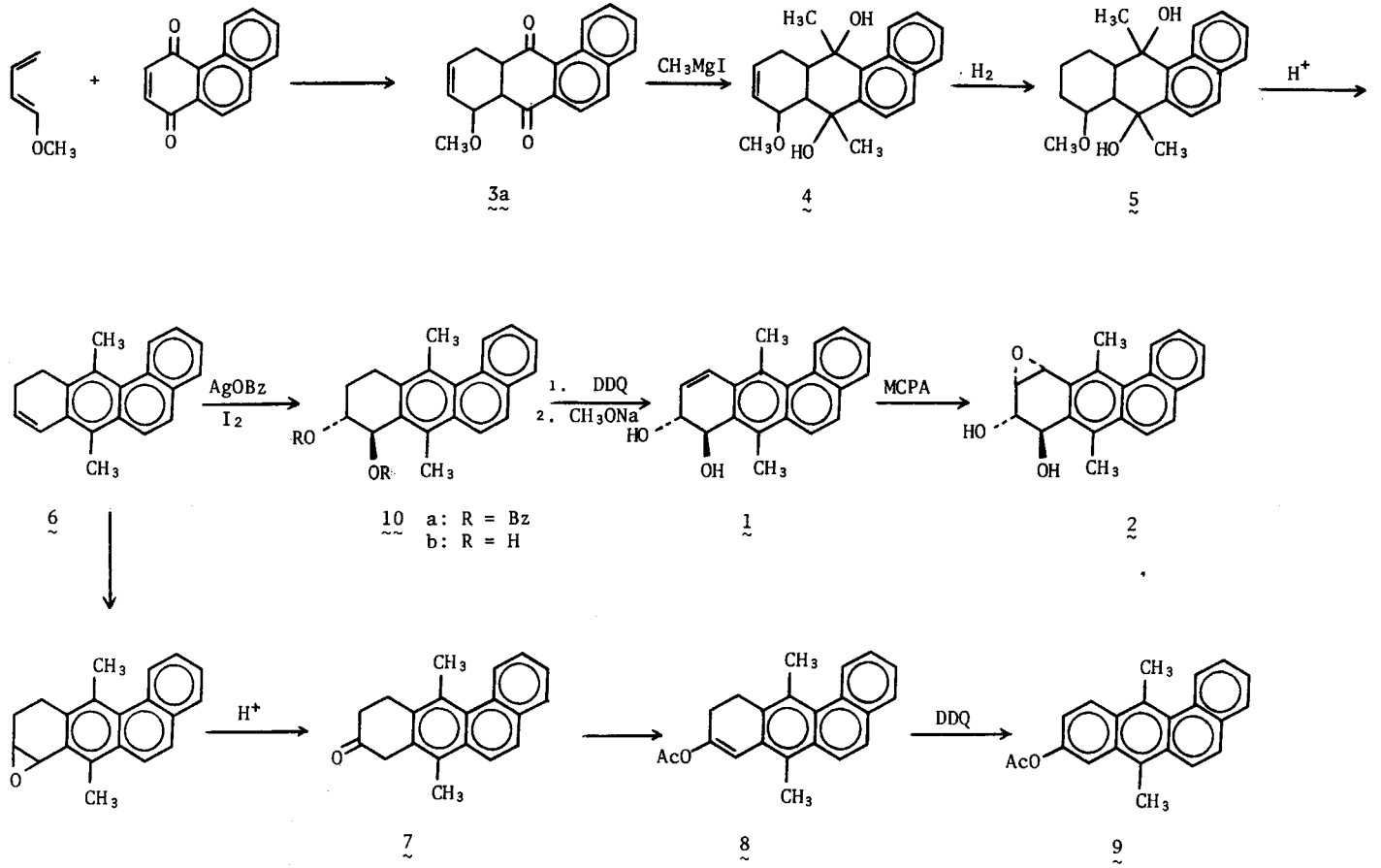
(Received in USA 30 June 1977; received in UK for publication 18 August 1977)

In view of the recent evidence implicating a diolepoxide derivative as the biologically active metabolite of the carcinogen benzo[a]pyrene,[1] it is important to determine the generality of this finding. However, the syntheses described for the benzo[a]pyrene[2] and benz[a]anthracene[3] diolepoxides are not conveniently applicable to the synthesis of the analogous derivatives of some of the most potent carcinogenic compounds, such as 7,12-dimethylbenz[a]anthracene (DMBA). The 8,9-dihydrodiol of DMBA (1), the probable metabolic precursor of the D-ring diolepoxide of DMBA (2), has been shown to be formed metabolically,[4] and 1 isolated from metabolic sources has been found to induce malignant transformation of mouse fibroblasts in culture[5] more effectively than DMBA itself; presumably 2 is the active metabolite.

Synthesis of 1 and 2 has now been achieved through the synthetic sequence depicted in Chart I. Diels-Alder reaction of 1-methoxybuta-1,3-diene (40% excess) with 17.5 g of phenanthrene-1,4-dione[6] in refluxing methanol (3 hr) gave a mixture of the isomeric 8- and 11-methoxy diketones, 3a,b, respectively (24.2 g). Recrystallization of the mixture from ether and from methanol furnished the pure 8-methoxy-diketone 3a (10.2 g),[7] mp 123.5-125.5°. Reaction of 3a with methyl Grignard reagent furnished the dialcohol 4. Hydrogenation of 4 (1.5 g in 50 ml ethyl acetate) over a Pd/C catalyst at 20 psig. gave 5 (mp 185-190.5°) which underwent dehydration with loss of methanol smoothly in refluxing benzene in the presence of *p*-toluenesulfonic acid to furnish directly the key intermediate 6 (mp 139-141°). The nmr spectrum[8] of 6, while

†*Trans*-8,9-dihydroxy-*anti*-10,11-epoxy-7,12-dimethyl-8,9,10,11-tetrahydrobenz[a]anthracene.

Chart I: Synthesis of DMBA diolepoxide



consistent with the 10,11-dihydro-DMBA structure, could not rule out the 8,9-dihydro-DMBA structure. The latter structure was excluded by the absence of any significant peaks in the UV spectrum above 320 nm as expected for this isomer by analogy with the corresponding 8,9- and 10,11-dihydrobenz[a]anthracene compounds.[3,9] This assignment was confirmed by conversion of 6 to the known[10] 9-acetoxy-DMBA (9) *via* epoxidation with *m*-chloroperbenzoic acid, BF_3-catalyzed isomerization to the 9-keto compound 7, conversion to the enol acetate 8 (mp 162-163°)[11] with isopropenyl acetate, and dehydrogenation with DDQ to 9 (mp 182.5-185°; lit.[10] 185-186°); the nmr spectrum of 9 proved identical to that of an authentic sample.

10,11-Dihydro-DMBA (6) was converted to *trans*-8,9-dihydroxy-8,9-dihydro-DMBA (1) *via* the procedures described earlier for synthesis of the related 8,9-dihydrodiol of benz[a]anthracene.[3a] Thus, Prévost reaction of 6 with silver benzoate and I_2 in refluxing benzene (65 hr) gave *trans*-8,9-dibenzoyloxy-8,9,10,11-DMBA[12] (10a)(mp 119-122°) in 98% yield; shorter reaction periods, as conventionally employed for reactions of this type, resulted in lower yields. Methanolysis of 10a with sodium methoxide in methanol provided the free diol, *trans*-8,9-dihydroxy-8,9,10,11-tetrahydro-DMBA (10b)(96% yield) which crystallized from acetone-triethylamine (19:1) as colorless prisms,[12] mp 196-197°. Dehydrogenation of 10a with an equimolar proportion of DDQ in refluxing dioxane (6 days) gave a mixture of *trans*-8,9-dibenzoyloxy-8,9-dihydro-DMBA (65%) and 10a. Separation was achieved by HPLC on LiChrosorb 10 μ at 75 psig eluted with CH_2Cl_2-pentane (4:1). Methanolysis of the dihydro dioldibenzoate furnished 1[13] in 96% yield. Finally, epoxidation of 1 with excess *m*-chloroperbenzoic acid in THF at ambient temperature provided 2 (40%); m/e (15 eV) 306; nmr ($CDCl_3$) δ 3.39 (dd,1,H_9), 3.93 (dd,1,H_{10}), 4.57 (d,1,H_{11}), and 4.90 ppm (d,1,H_8); $J_{8,9}$ = 7 Hz, $J_{9,10}$ = 2 Hz, $J_{10,11}$ = 4 Hz.

Synthesis of the isomeric 10,11-dihydrodiol of DMBA and the corresponding *anti*-DMBA diol-epoxide from the 11-methoxy-diketone 3b is currently in progress.

Preliminary tests indicate that 2 inhibits the infectivity of the ØX 174 DNA virus through direct interaction with the viral nucleic acid to an extent approximating that of the analogous *anti*-BA-diolepoxide.[14] Evaluation of the carcinogenic and mutagenic activity of 2 is also currently under investigation.

Acknowledgement: This investigation was supported by grant CA 11968 from the National Cancer Institute, DHEW.

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7. All new compounds gave satisfactory microanalysis for C,H within ± 0.3% and/or mass spectra and nmr and other spectra consistent with the assigned structure.
8. Nmr: ($CDCl_3$) δ 2.1-2.7 (m,2,H_{10}), 2.75 (s,3,CH_3), 2.95 (s,3,CH_3), 2.7-3.1 (m,2,H_{11}), 6.32 (d of t,1,$J_{8,9}$ = 10 Hz,$J_{9,10}$ = 4 Hz,H_9), 7.10 (d of t,1,$J_{8,9}$ = 10 Hz,$J_{8,10}$ = 2 Hz), 7.47-8.20 (m,5, aromatic), and 8.46-8.76 ppm (m,1,H_1).
9. The UV spectrum of 6 in CH_3OH showed maxima at 245, 272, 280, and 306 nm. Its pattern closely resembled that of 10,11-dihydro-BA and differed from that of 8,9-dihydro-BA.[3c]
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11. Nmr of 8: ($CDCl_3$) δ 2.17 (s,3,CH_3CO), 2.57 (s,3,CH_3), 2.77 (s,3,CH_3), 6.63 (s,1,H_8).
12. Nmr of 10a: ($CDCl_3$) δ 2.67 (s,3,7-CH_3), 2.30-2.70 (m,2,H_{10}); 2.98 (s,3,12-CH_3), 2.80-3.05 (m,2,H_{11}), 5.78 (m,1,H_9), 6.73 (d,1,$J_{8,9}$ = 3 Hz,H_8), 7.20-8.10 (m,15, aromatic), and 8.58 ppm (m,1,H_1); m/e (70 eV) 500. Nmr of 10b: δ 2.0 (m,2,H_{10}), 2.80 (s,3,7-CH_3), 2.82 (m,2, H_{11}), 2.82 (s,3,12-CH_3), 4.12 (m,1,H_9), 5.0 (d,1,$J_{8,9}$ = 4 Hz,H_8), 7.37-8.02 (m,5, aromatic), and 8.45 ppm (m,1,H_1); m/e (70 eV) 292.
13. The UV spectrum of 1 (CH_3OH) showed maxima at 265, 304, 313, 330, and 350 nm; the UV pattern closely resembled that of *trans*-8,9-dihydroxy-8,9-dihydro-BA[3a,c] shifted ~ 10 nm to longer wavelength. Nmr of 1: ($CDCl_3$) δ 2.98 (s,3,7-CH_3), 3.20 (s,3,12-CH_3), 4.40 (dd,1,$J_{8,9}$ = $J_{9,10}$ = 6 Hz,H_9), 5.20 (d,1,$J_{8,9}$ = 6 Hz,H_8), 6.28 (dd,1,$J_{9,10}$ = 6 Hz,$J_{10,11}$ = 10 Hz,H_{10}), 7.20 (d,1,$J_{10,11}$ = 10 Hz,H_{11}), 7.35-8.17 (m,5, aromatic), and 8.50 ppm (m,1,H); m/e (70 eV) 290.
14. W. T. Hsu, R. G. Harvey, E. J. Lin, and S. B. Weiss. *Proc. Nat. Acad. Sci. USA*, 74, 1378 (1977); W. T. Hsu, E. J. Lin, R. G. Harvey, and S. B. Weiss, *Ibid*, in press.