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SYNTHESIS OF DIHYDRODIOLS FROM CHRYSENE AND DIBENZO[a,h]ANTHRACENE

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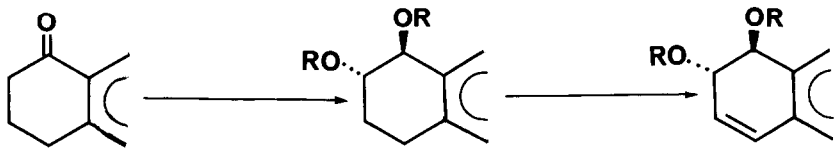
Numerous lines of evidence have now implicated 7,8-diol-9,10-epoxides as metabolically formed ultimate carcinogens from the environmental contaminant benzo[a]pyrene.[1,2] In an attempt to generalize the concept of diol epoxides[3] as ultimate carcinogens, we have attempted to predict which of the several possible diol epoxides of a given polycyclic hydrocarbon would show the highest biological activity. Comparison of existing carcinogenicity data for alkyl and halogen substituted hydrocarbons[4] as well as perturbational molecular orbital calculations[5] predict that diol epoxides on saturated angular benzo-rings in which the epoxide forms part of the "bay-region" of the hydrocarbon[6] will have the highest biological activity. To test this prediction, we have recently synthesized dihydrodiols[7] and diol epoxides[8] of benzo[a]-anthracene. Studies of the mutagenicity[9,10] and carcinogenicity[11] of these compounds have born out the prediction in that the 3,4-dihydrodiol and its diol epoxides were markedly more active than the other isomeric dihydrodiols, diol epoxides, or the parent hydrocarbon. The present report describes the synthesis of dihydrodiols from chrysene and dibenzo[a,h]anthracene in order to further test the "bay-region" theory.

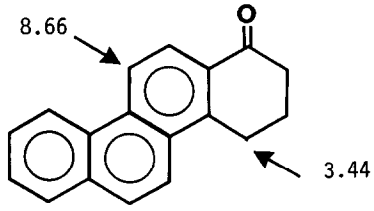
A general approach which has been successfully utilized in the synthesis of dihydrodiols from polycyclic hydrocarbons[7,12,13] is shown below:



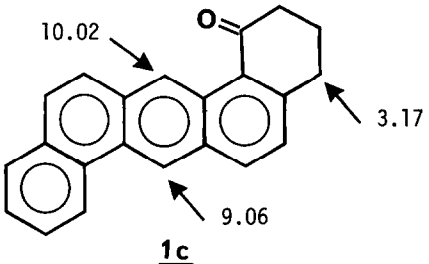
1a-d **2a-d** **3a-d**

In order to apply this approach, ketones related to chrysene and dibenzo[a,h]anthracene were required. Of these the 1-keto-(1a)[14] and 4-keto-1,2,3,4-tetrahydrochrysene (1b)[15] and 1-keto-1,2,3,4-tetrahydrodibenzo[a,h]anthracene (1c)[16] were known. In order to synthesize the remaining 4-keto-1,2,3,4-tetrahydrodibenzo[a,h]anthracene (1d), 8-keto-8,9,10,11-tetrahydrobenzo[a]-anthracene[17] was converted to 4-(8-benzo[a]anthryl)-butyric acid (mp 167-169°, 39% overall yield from ketone) in a manner analogous to that used in the synthesis of 4-(1-phenanthryl)-butyric acid.[14] The procedure consisted of a Reformatsky reaction between the ketone and methyl

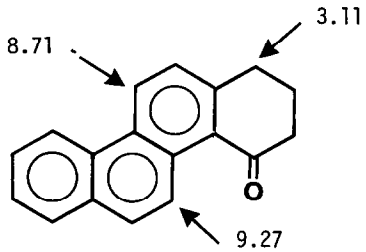
bromocrotonate, dehydration of the resultant alcohol to a diene ester, and isomerization to the aryl butyric acid with KOH in refluxing ethylene glycol. The desired ketone (1d) was obtained by cyclization of its acid chloride with $SnCl_4$ (70% yield, mp 247-248°). Resynthesis of ketone 1c[16] (mp 168-169°) also used methyl bromocrotonate. Diagnostic pmr signals (δ) at 220 MHz ($CDCl_3$) are shown on the structures of the ketones.



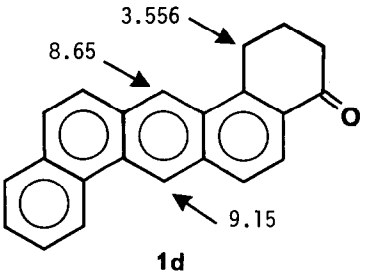
1a



1c



1b



1d

The four ketones (1a-1d) were reduced, dehydrated, and converted into trans diesters on the saturated terminal rings. Bromination (NBS) and dehydrobromination (DBN) furnished the desired dihydrodiol diesters (Table I). The pmr spectra of these diesters (Table II) are consistent with previously reported spectra for related compounds.[7,13,18] Those hydrogens for which signals are not reported are buried in the aromatic envelope due to edge deshielding in the "bay-region". In addition, the uv spectra of the dihydrodiols (Figure 1) obtained on hydrolysis are nearly identical to the corresponding dihydroaromatic hydrocarbons.

Thus far we have completed studies of the ability of drug metabolizing enzymes to activate the chrysene dihydrodiols to mutagens and have found that the 1,2-dihydrodiol with the "bay-region" double bond is activated to mutagens to a 20-fold greater extent than is chrysene or the 3,4- and 5,6-dihydrodiols.[19] Preliminary studies with the dihydrodiols from dibenzo[a,h]-anthracene indicate that the 3,4-dihydrodiol with a "bay-region" double bond at the 1,2-position is most strongly activated. The present results taken together with reports that the metabolically-induced binding of 7-methyl- and 7,12-dimethylbenzo[a]anthracene to DNA involves the 1,2,3,4-positions of these hydrocarbons provides strong support for the "bay-region" theory. The same approach which allowed synthesis of the required ketones from dibenzo[a,h]anthracene has worked with higher yields in the synthesis of 1- and 4-keto-1,2,3,4-tetrahydrodibenzo[a,j]-anthracene[20] from 11-keto-8,9,10,11-tetrahydrobenzo[a]anthracene. The isomeric dihydrodiols from the [a,j] isomer are presently being synthesized. Comparison of the biological activity of the isomeric dihydrodiols from dibenzo[a,h] and [a,j]anthracene will provide a key test of the "bay-region" theory since the [a,h] isomer is a potent carcinogen while the [a,j] isomer is quite weak.

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TABLE I Conversion of ketones into dihydrodiol diesters[a]

tetrahydro ketone[b]	tetrahydro diester (2a-2d)[c]	dihydrodiol diester (3a-3d)[d]
1a	66% as diacetate (mp 168°)	24% (mp 176-177°)
1b	46% as dibenzoate (mp 116-117°)	45% (mp 86-87°)
1c	60% as dibenzoate (mp 164-166°)	31% (glass)
1d	40% as diacetate (mp 195-196°)	22% (mp 183-185°)

[a]All compounds in the present study gave acceptable nmr and mass spectra. Those for which mp are reported were pure by combustion analysis. [b]Yields for reduction and dehydration were generally 90-95% except in the case of ketone 1d which on dehydration of the alcohol occasionally led to ~30% fully aromatic hydrocarbon by autoxidation. [c]Yields for Prevost reaction [d]Overall yields for bromination-dehydrobromination. Diazabicyclononane was used to remove HBr in all cases. Diacetates were hydrolyzed with NH_3CH_3OH and dibenzoates with methoxide/$HOCH_3$ in essentially quantative yields.

TABLE II PMR spectra (100 MHz, $CDCl_3$) of dihydrodiol diesters

dihydrodiol	benzylic ester	non-benzylic ester	benzylic vinyl	non-benzylic vinyl
3a (diacetate)	H_1 6.38	H_2 5.67	H_4 ---	H_3 6.26
	($J_{1,2}$ = 6.5, $J_{3,4}$ = 10.0, $J_{2,3}$ = 4.0), acetates at 2.06 and 2.14			
3b(dibenzoate)	H_4 ---	H_3 5.93	H_1 7.05	H_2 6.45
	($J_{1,2}$ = 10.0, $J_{2,3}$ = 5.5, $J_{3,4}$ = 1.8)			
3c (dibenzoate)	H_1 ---	H_2 5.91	H_4 7.04	H_3 6.48
	($J_{1,2}$ = 1.8, $J_{2,3}$ = 5.5, $J_{3,4}$ = 10.0)			
3d (diacetate)	H_4 6.40	H_3 5.71	H_1 ---	H_2 6.32
	($J_{1,2}$ = 10.0, $J_{2,3}$ = 4.0, $J_{3,4}$ = 5.8), acetates at 2.06 and 2.14			

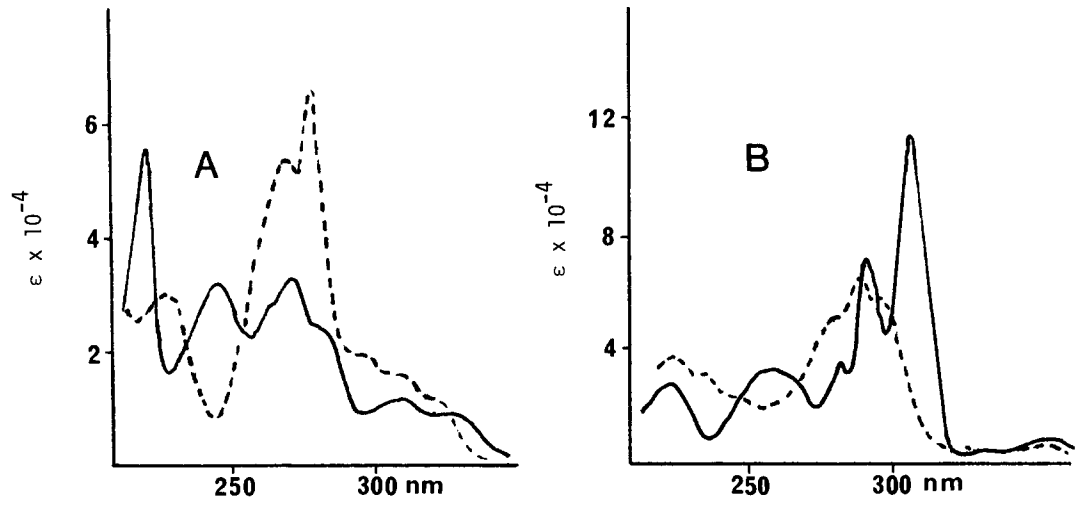

FIGURE 1. Ultraviolet spectra (CH_3OH) of isomeric trans dihydrodiols from chrysene (A) and

Fig. 1 (Cont.) dibenzo[a,h]anthracene (B): chrysene 1,2-[——; λ_{max} (ε), 221 (54,900)] and 3,4-isomer [----; λ_{max} (ε), 278 (64,260)]; dibenzo[a,h]anthracene 1,2-[——; λ_{max} (ε), 306 (110,500)] and 3,4-isomers [----; λ_{max} (ε), 278 (63,300)]. The corresponding "K-region" dihydrodiols had the following maxima: trans-5,6-dihydroxy-5,6-dihydrochrysene [λ_{max} (ε), 262 (104,500)] and trans-5,6-dihydroxy-5,6-dihydrodibenzo[a,h]anthracene [λ_{max} (ε), 279 (60,100)].

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20. The pmr spectrum ($CDCl_3$) of the 1-keto isomer (mp 126-127°) has the methylene hydrogens at C-4 at 3.14 δ and H_{14} at 10.93 δ while the 4-keto isomer (mp 204-206°) has the methylene hydrogens at C-1 at 3.40 δ and H_{14} at 9.21 δ.