We hope that this new synthetic procedure will stimulate interest in cyanoformates.

Experimental Section

Many of these cyanoformates are known compounds; however, spectral properties even on those that are known are meager. For this reason, ir and NMR spectra of all compounds are reported here. The new cyanoformates, *n*-butyl, isobutyl, 2,2,2-trichloroethyl, and 2-octyl, have been analyzed. Infrared spectra were obtained on a Perkin-Elmer 337 spectrometer and were calibrated against known bands in a polystyrene film. NMR spectra were recorded on a Varian T-60 spectrometer. Ten percent solutions in carbon tetrachloride with tetramethylsilane as internal standard were used. Vapor phase chromatography was carried out on a Hewlett-Packard F & M 700 using a 20% polyphenyl ether on Chromosorb P 4 ft × 0.25 in. column. Microanalysis was performed by Elek Microanalytical Laboratories, Torrance, Calif. Boiling points and melting points were not corrected.

Preparation of Isobutyl Cyanoformate. In a 50-ml round-bottom flask equipped with a reflux condenser, nitrogen inlet, and a Teflon-covered magnetic stirring bar was placed 30 ml of methylene chloride, 3.5 g (0.054 mol) of potassium cyanide, 6.8 g (0.05 mol) of isobutyl chloroformate (Eastman), and approximately 50 mg (0.02 mmol) of 18-crown-6.[18] The mixture was stirred at room temperature. The reaction could be followed by ir (the disappearance of the band at 1790 cm^{-1} due to the C=O of the starting chloroformate and the appearance of bands at 2250 cm^{-1} due to the C≡N and at 1750 cm^{-1} due to the C=O of the product cyanoformate) or by GLC (the starting material had a shorter retention time than the product cyanoformate in all cases which were examined). When the starting material had disappeared (~4 h), the solution was filtered. The solution was distilled through a 15-cm Vigreux column. Solvent was removed at atmospheric pressure. A fraction consisting of pure isobutyl cyanoformate by GLC, 6.0 g (0.047 mol), 94% yield, distilled at 52–53 °C (20 mm): NMR d (2 H) δ 4.1, J = 7 Hz, m (1 H) 2.1, d (6 H) 1.0, J = 7 Hz; ir 2250 C≡N, and 1750 cm^{-1} C=O. Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 56.70; H, 7.03.

All other cyanoformates reported were prepared in analogous fashion.

Methyl cyanoformate from methyl chloroformate (Aldrich): NMR s (3 H) δ 4.0; ir 2250 C≡N, 1750 cm^{-1} C=O.

Ethyl cyanoformate from ethyl chloroformate (Aldrich): NMR q (2 H) δ 4.4, J = 7 Hz, t (3 H) 1.4, J = 7 Hz; ir 2250 C≡N, and 1750 cm^{-1} C=O.

***n*-Butyl cyanoformate** from *n*-butyl chloroformate (Aldrich): NMR t (2 H) δ 4.4, J = 7 Hz, multiplets (7 H) 1.7–1.0; ir 2250 C≡N, and 1750 cm^{-1} C=O. Anal. Calcd for $C_6H_9O_2N$: C, 56.68; H, 7.14. Found: C, 57.01; H, 7.10.

2,2,2-Trichloroethyl cyanoformate from 2,2,2-trichloroethyl chloroformate (Aldrich): NMR s (2 H) δ 4.75; ir 2250 C≡N, and 1760 cm^{-1} C=O. Anal. Calcd for $C_4H_2O_2NCl_3$: C, 23.73; H, 1.00. Found: C, 23.87; H, 1.32.

Isopropyl cyanoformate from isopropyl chloroformate (Research Organic/Inorganic Chemical Co.): NMR septet (1 H) δ 5.2, J = 7 Hz, d (6 H) 1.4, J = 7 Hz; ir 2250 C≡N, 1750 cm^{-1} C=O.

2-Octyl cyanoformate from 2-octyl chloroformate which had been prepared by reaction of 2-octyl alcohol with phosgene:[24] NMR m (1 H) δ 5.1, m (16 H) 1.3; ir 2250 C≡N and 1745 cm^{-1} C=O. Anal. Calcd for $C_{10}H_{17}O_2N$: C, 65.54; H, 9.35. Found: C, 65.51; H, 9.31.

Cyclohexyl cyanoformate from cyclohexyl chloroformate which had been prepared by reaction of cyclohexanol with phosgene:[24] NMR br (1 H) δ 5.0, m (10 H) centered at 1.6; ir 2245 C≡N, and 1745 cm^{-1} C=O.

Benzyl cyanoformate from benzyl chloroformate (Aldrich): NMR s (5 H) δ 7.2, s (2 H) 5.0; ir 2245 C≡N, and 1745 cm^{-1} C=O.

Phenyl cyanoformate from phenyl chloroformate (Eastman): NMR m (5 H) δ 7.3; ir 2250 C≡N, and 1760 cm^{-1} C=O.

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Registry No.—Isobutyl cyanoformate, 59873-30-2; isobutyl chloroformate, 543-27-1; methyl cyanoformate, 17640-15-2; methyl chloroformate, 79-22-1; ethyl cyanoformate, 623-49-4; ethyl chloroformate, 541-41-3; *n*-butyl cyanoformate, 5532-84-3; *n*-butyl chloroformate, 592-34-7; 2,2,2-trichloroethyl cyanoformate, 59873-31-3; 2,2,2-trichloroethyl chloroformate, 17341-93-4; isopropyl cyanoformate, 59873-32-4; isopropyl chloroformate, 108-23-6; 2-octyl cyanoformate, 59873-33-5; 2-octyl chloroformate, 15586-11-5; cyclohexyl cyanoformate, 5532-84-4; cyclohexyl chloroformate, 13248-54-9; benzyl cyanoformate, 5532-86-5; benzyl chloroformate, 501-53-1; phenyl cyanoformate, 5532-82-1; phenyl chloroformate, 1885-14-9; potassium cyanide, 151-50-8.

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An Unusual Arene Oxide Reaction. Solvent Capture during Acid-Catalyzed Solvolysis of 7,12-Dimethylbenz[*a*]anthracene 5,6-Oxide

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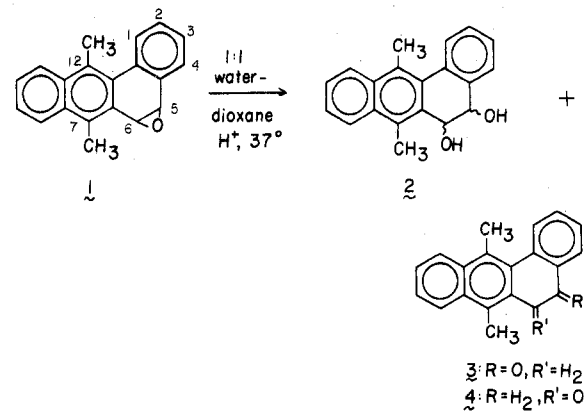
Recent interest in polycyclic arene oxides as mediators of polycyclic arene carcinogenesis[2] has prompted us to study the aqueous solvolysis of 7,12-dimethylbenz[*a*]anthracene 5,6-oxide (**1**), a K-region[3] metabolite[4] of the carcinogenic 7,12-



1 **2**

3: R = O, R' = H_2
4: R = H_2, R' = O

Table I. Product and Rate Data for the Reaction of 7,12-Dimethylbenz[a]anthracene 5,6-Oxide (1) in Acidic 1:1 Dioxane-Water (v/v), 0.10 M in KCl at 36.8 °C

Reaction pH[a]	$k_{obsd} \times 10^4$, s^{-1}	Yield[b] % 5 + 6 ketones	Cis dihydrodiols	Trans dihydrodiols
1.0		25	8	67
3.0		24	9	67
5.0		20	11	69
5.50	22.2	27	10	63
5.90	12.4	25	9	66
6.20	5.67			
6.60	2.44	33	16	51
7.0		25	14	61

[a] By glass electrode. [b] Integration of HPLC traces with correction for ϵ_{254} values.

Table II. Comparison of the Product and Rate Data on 7,12-Dimethylbenz[a]anthracene 5,6-Oxide with Related Benz[a]anthracene Oxides Not Containing Bay-Position Methyl Groups. Reactions Conducted in 1:1 Dioxane–Water 0.10 M in KCl at 37 °C

K-Region arene oxide	k^{H},[c] $M^{-1} \times 10^{-1}$	Dihydrodiol yield, %	Cis/trans ratio of dihydrodiols	Rearrangement products
Benz[a]anthracene 5,6-oxide (5)[a]	1.5	25	31/69	Phenols
3-Methylcholanthrene 11,12-oxide (6)[a]	99	25	75/25	Phenols
7,12-Dimethylbenz-[a]anthracene 5,6-oxide (1)[b]	90	75	15/85	Ketones

[a] Data from ref 5. [b] Data from this work. [c] Specific acid catalyzed rate constant.

dimethylbenz[a]anthracene. We report here that in acid-catalyzed reactions, oxide 1 shows unusually high electrophilicity toward water, as compared to several previously studied K-region arene oxides.[5] Treatment of 1 with aqueous dioxane containing dilute acid produced mostly K-region dihydrodiols, 2, along with some K-region ketones, 3 and 4. In contrast, we previously found that under the same conditions the K-region oxides of phenanthrene, benz[a]anthracene (5), dibenz[a,h]anthracene, and 3-methylcholanthrene (6) all gave high yields of K-region phenols with lesser amounts of K-region dihydrodiols.[5]

Oxide 1 was maintained at constant pH with dilute HCl in a pH stat at 37 °C in 1:1 dioxane–water (v/v), 0.10 M in KCl. After all the oxide had reacted, the products were analyzed by high-pressure liquid chromatography (HPLC). Eluted peaks were identified as K-region dihydrodiols, 2, and ketones, 3 and 4, by comparison of their retention volumes and ultraviolet spectra with those of authentic samples.[6-9] HPLC of the ketones from reaction of oxide 1 at pH 5.0 showed that the 5 ketone, 3, and the 6 ketone, 4, were produced in the ratio of 2:3, respectively. Product yields as a function of pH are summarized in Table I. Control experiments showed that under these reaction and analysis conditions the dihydrodiols are stable. The 75% yield of dihydrodiols is strikingly different from the 25% dihydrodiol yields we obtained from the reaction of several other arene oxides.[5] The cis/trans ratio of the dihydrodiols obtained from 1 was 15/85; this is much lower than that obtained from 3-methylcholanthrene 11,12-oxide

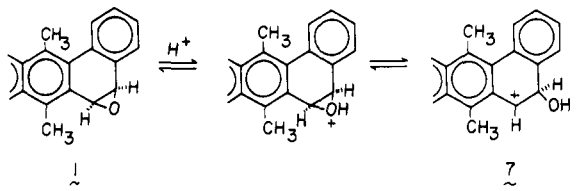
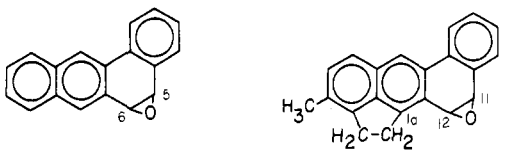


Figure 1. Generation of a benzylic cation, 7, by reversible protonation of the oxirane oxygen followed by scission of the C_6–O bond.

(6), and is even lower than that obtained from benz[a]anthracene 5,6-oxide (5) (Table II). K-Region phenols, the major solvolysis product of the previously studied oxides,[5] could not be detected.



The kinetics of the solvolysis reaction at 36.8 °C were monitored spectrophotometrically. The k_{obsd} values for the first-order disappearance of oxide 1 are proportional to $[H^+]$ in the pH range 5–7 (Table I); the proportionality constant k_H is 900 M^{-1} s^{-1}. The pH–rate profile in this pH range is nearly identical with that of 3-methylcholanthrene 11,12-oxide (6),[5,10] and is consistent with reversible protonation of the oxirane oxygen, followed by rate-limiting ring opening to an intermediate cation (for example, 7 in Figure 1).[5,11] Product formation then occurs rapidly either by attack of water or rearrangement, followed by proton loss.

The formation of cations analogous to 7 from different arene oxides occurs at different rates, according to the ability of the attached aryl groups to stabilize the incipient positive charge at the benzylic carbon.[5] It was shown in our previous work that there was a positive correlation between the k_H value for a given oxide and the cis/trans ratio of the product dihydrodiols.[5] This is so because of the large amount of positive charge delocalized throughout the carbons of both the rate-limiting ring opening and the cis-addition transition states, whereas the positive charge density on the carbons of the trans-addition transition state is much lower.[5] Thus, solvolysis of 7,12-dimethylbenz[a]anthracene 6-oxide (1) would, on electronic grounds, be expected to produce nearly the same cis/trans ratio as 6. In fact, however, the ratio from 1 is 15-fold lower.

We have previously observed K-region dihydrodiols as products of acid-catalyzed solvolysis of arene oxides in 1:1 dioxane–water, 0.10 M in KCl.[5] In solvent water at pH 6–7, phenanthrene 9,10-oxide and several alkylated benzene oxides also produce high yields of dihydrodiol.[12,13] The trans dihydrodiol yields reported here, which are higher than we previously found,[5] may be related to the strain inherent in the 7,12-dimethylbenz[a]anthracene 5,6-oxide system. Glusker et al.[14] have shown by x-ray diffraction that in the crystal, the phenyl ring of oxide 1 (carbon 1–4, 1a, and 4a) is twisted such that there is a dihedral angle of 28° between the phenyl and naphthyl rings (Figure 2). This twist may have two related effects: (1) it may cause the observed high rate of acid-catalyzed ring opening due to increased strain in the oxirane ring, and (2) it may largely prevent cis attack of water due to decreased conjugative interaction between the K-region carbons and the aryl moieties.

The dihedral twist present in the ions from 1 may cause the observed low yield of rearrangement products by retarding the NIH shift,[15] because the twist may inhibit full cyclic

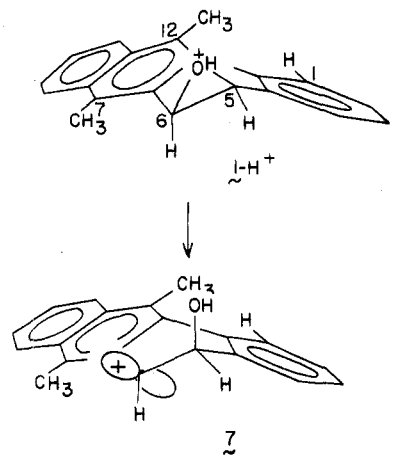


Figure 2. Formation of cation 7 from the twisted arene oxide 1.

conjugation in the NIH shift transition state,[5] or cause the reacting C–H bond to overlap less with the adjacent empty p orbital.

The production of K-region ketones instead of phenols from solvolysis of 1 is a related phenomenon. Most arene oxides would be expected to rearrange by the NIH shift to ketones and rapidly tautomerize to the more stable phenolic form.[15] Phenols are usually more stable because the endocyclic double bond becomes delocalized as a result of conjugation with the neighboring aromatic groups.[16] However, in the case of 5- and 6-hydroxy-7,12-dimethylbenz[*a*]anthracenes, the noncoplanarity of the K-region endocyclic bond with the attached aryl groups should inhibit the full cyclic delocalization required for phenol stability.[9,17] Indeed, it has been found that the 5 and 6 ketones are more stable than the respective phenols, and that the phenol–ketone tautomerization occurs only under conditions much more vigorous than we used (at 90 °C in 0.01 M HCl, $t_{1/2}$ = 10 h).[8] Thus, ketones 3 and 4 are primary products of solvolysis that are formed by NIH shifts of cationic intermediates, but do not undergo the usual tautomerization because of steric destabilization of the phenols. In contrast, the phenols derived from rearrangement of benz[*a*]anthracene 5,6-oxide (5) and 3-methylcholanthrene 11,12-oxide (6) are more stable than the respective ketones because the nearly planar aromatic ring systems[18,19] allow delocalization of the endocyclic K-region double bonds.

The foregoing results illustrate the profound effects which a substituent distal to the oxirane ring can have on the solvolytic reactivity of an arene oxide. However, the relationship of these results to the biological effects of 7,12-dimethylbenz[*a*]anthracene 5,6-oxide or its parent hydrocarbon remains to be determined.

Experimental Section

Materials. Dioxane was purified by the method of Fieser.[20] It was mixed with an equal volume of double-distilled water, 0.200 M in KCl, sealed under nitrogen in 250-ml bottles, and stored at −20 °C. All other solvents were Spectrograde or were distilled before use. *cis*-5,6-Dihydro-5,6-dihydroxy-7,12-dimethylbenz[*a*]-anthracene was synthesized by osmium tetroxide oxidation of the parent hydrocarbon;[17] *trans*-5,6-dihydro-5,6-dihydroxy-7,12-dimethylbenz[*a*]-anthracene was synthesized by lithium aluminum hydride reduction of the 5,6-quinone in ether followed by column chromatographic separation (Florisil and benzene–ethanol) of the cis and trans dihydrodiols.[17] The oxide, 1, was synthesized by treatment of the trans dihydrodiol with dimethylformamide dimethyl acetal in benzene at reflux.[17] The K-region ketones were synthesized by dehydration of the cis dihydrodiol in refluxing acetic acid–HCl, followed by Florisil–benzene column chromatography.[8]

Spectra. Uv spectra were recorded on a Cary 15 spectrophotometer.

High-Pressure Liquid Chromatography. A Du Pont Model 830 chromatograph equipped with a Zorbax (silica) column (0.25 m × 2.2 mm i.d.) and a 254-nm photometric detector was used. Elution of a reaction aliquot with 1:1 (v/v) hexane–(dichloromethane, 2-propanol, acetic acid; 1000:20:0.1) produced peaks at 8 ml (ketones 3 and 4), 35 ml (cis dihydrodiol), and 80 ml (trans dihydrodiol). Integration was by multiplication of peak height by peak width at half height; a correction for the different ϵ value at 254 nm was applied for the ketone peak.[8] Elution of a reaction aliquot with the upper layer of 25:1:0.2 (v/v) hexane–dioxane–formic acid produced peaks due to the 6 ketone, 4 (2.4 ml) and the 5 ketone, 3 (2.8 ml), in addition to the dihydrodiol peaks.

Rate Measurements. Kinetics were performed similarly to previous experiments.[5] Reactions were run in a 20-ml stirred reactor thermostated at 36.8 ± 0.05 °C and kept at constant pH by a Radiometer pH stat. Aliquots were removed by automatic pipet and immediately quenched in dioxane–water containing sodium bicarbonate. The absorbance of each quenched aliquot was read at 277.0 nm, a λ_{max} of oxide 1; rate constants were obtained graphically from plots of ln $(A_t - A_\infty)$ vs. time.

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Registry No.—1, 39834-38-3; *cis*-2, 2518-02-7; *trans*-2, 16644-15-8; 3, 53306-07-3; 4, 55327-65-6.

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