Ozonolysis of Polycyclic Aromatics. X.[1] 7,12-Dimethylbenz[a]anthracene[2]

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Received January 16, 1963

Ozonization of 7,12-dimethylbenz[a]anthracene (1) in methylene chloride, 3:1 methylene chloride–methanol, and acetone gave an unstable peroxidic mixture, oxidation of which with hydrogen peroxide and silver oxide led to benz[a]anthracene-7,12-dione, 1,2-anthraquinonedicarboxylic acid, phthalic acid, 1,4-dimethyl-3-hydroxymethyl-2-phenylnapthalene-2′-carboxylic acid, and, most probably, 1,2-diacetylnaphthalene. Thus, L-region reactivity to ozone is decreased in the potent carcinogen 1, relative to benz[a]anthracene, while simultaneous K-region cleavage is increased as would be predicted from the Pullmans' K-region theory of carcinogenesis.

The quantum–mechanical (K-region) theory of carcinogenesis[3] has been an extraordinary stimulus to research in the chemical reactivity of that most important and probably most studied class of carcinogens, the unsubstituted polycyclic aromatic hydrocarbons.[4] Despite recent criticism of the theory,[5] it seems generally accepted that the observation of any consistent correlation of the carcinogenicity (or lack of it) of these polycyclic aromatic hydrocarbons, with some specific chemical reaction would necessarily be "considered as extremely significant for the process of carcinogenesis itself."[3d] All previous studies of chemical reactivity of these *unsubstituted* polycyclic aromatic hydrocarbons have concerned themselves mainly with addition or substitution reactions involving either reactive centers (L-region) or reactive bonds (K-region).[3d] It also has been predicted that "most probably no consistent general relation exists between these reactions and the carcinogenic activity of *substituted* molecules.[3e]

With ozone, work in our laboratory and others has shown that reaction occurs with all carcinogenic and noncarcinogenic, unsubstituted polycyclic aromatics examined to date, and most importantly, reaction can occur uniquely at any of the three relevant sites, K-, L-, and M-regions.

Thus ozone attacks: (i) the K-region predominantly in phenanthrene,[6a,7a,8a] chrysene,[9a] triphenylene,[9a] pyrene,[9b,10] dibenz[a,h]anthracene,[6b] dibenz[a,j]anthracene,[1,11] benzo[g]chrysene,[9a] picene,[9a] and dibenz[c,g]-phenanthrene[9a]; (ii) the L-region predominantly in anthracene,[7b,9c,12] naphthacene,[6c,9c] benz[a]anthracene,[6d,9a,12] and perylene[9d]; (iii) the L- and M-regions in benzo[a]pyrene.[6e] Where measurable, we also have demonstrated that ozone reacts predominantly at those positions in an unsubstituted polycyclic aromatic whose corresponding *o*- or *p*-quinone had the lowest corrected oxidation–reduction potential.[6f,13,14]

Strikingly fewer ozonization data are available for methyl-substituted polycyclic aromatics. The ozonization of 1- and 2-methylnaphthalenes,[17] and 2,3- and 1,4-dimethylnaphthalenes[8b] in general led to complex product mixtures, and the separable components were obtained only in poor yields. Methyl groups undoubtedly activate the ring to which they are attached,[18] but their "leaving power"[7d] to ozone attack is low, and in 9,10-dimethylanthracene, the initial zwitterionic intermediate formed by addition of ozone, stabilizes itself by forming the 9,10-transannular ozonide with ring-methyl groups intact.[7d] In this paper, we report on the ozonization of the potent (++++) carcinogen,[19] 7,12-dimethylbenz[a]anthracene (1).

Results

Ozonization of 1 dissolved in methylene chloride, 3:1 methylene chloride–methanol, and acetone was

(1) Paper IX, E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *J. Org. Chem.*, **27**, 3618 (1962).

(2) This research was supported by a grant C-3325(C4) from the U. S. Public Health Service, National Cancer Institute.

(3) (a) A. Pullman and B. Pullman, "Cancérization par les Substances Chimiques et Structure Moléculaire," Masson et Cie, Paris, 1955; summaries in "Advances in Cancer Research," Academic Press Inc., New York, N. Y.; (b) C. A. Coulson, Vol. I, 1953, p. 2; (c) G. M. Badger, Vol. II, 1954, p. 73; (d) A. Pullman and B. Pullman, Vol. III, 1955, p. 117; (e) p. 154.

(4) J. R. Sampey, *J. Chem. Educ.*, **32**, 448 (1955).

(5) "Theories of Carcinogenesis," I. Hieger in "Carcinogenesis, Mechanisms of Action," Ciba Foundation Symposium, Little, Brown and Co., Boston, Mass., 1958, pp. 3–11. See B. Pullman's reply in "Berliner Symposium über Fragen der Carcinogenese," Akademie-Verlag, Berlin, 1960, p. 69.

(6) (a) W. J. Schmitt, E. J. Moriconi, and W. F. O'Connor, *J. Am. Chem. Soc.*, **77**, 5460 (1955); (b) E. J. Moriconi, W. F. O'Connor, W. J. Schmitt, G. W. Cogswell, and B. P. Fürer, *ibid.*, **82**, 3441 (1960); (c) E. J. Moriconi, W. F. O'Connor, and L. B. Taranko, *Arch. Biochem. Biophys.*, **83**, 283 (1959); (d) E. J. Moriconi, W. F. O'Connor, and F. T. Wallenberger, *J. Am. Chem. Soc.*, **81**, 6466 (1959); (e) E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *ibid.*, **83**, 4618 (1961); (f) E. J. Moriconi, B. Rakoczy, and W. F. O'Connor, *J. Org. Chem.*, **27**, 2772 (1962).

(7) (a) P. S. Bailey, *J. Am. Chem. Soc.*, **78**, 3811 (1956); (b) F. Dobinson and P. S. Bailey, *Tetrahedron Letters*, No. **13**, 14 (1960); (c) F. Dobinson and P. S. Bailey, *Chem. Ind.* (London), 632 (1961); (d) R. E. Erickson, P. S. Bailey, and J. C. Davis, Jr., *Tetrahedron*, **18**, 389 (1962).

(8) (a) J. P. Wibaut and Th. J. De Boer, *Rec. trav. chim.*, **78**, 183 (1961); (b) L. W. F. Kampschmidt and J. P. Wibaut, *ibid.*, **73**, 431 (1954).

(9) (a) P. G. Copeland, R. E. Dean, and D. McNeil, *J. Chem. Soc.*, 1232 (1961); (b) *Chem. Ind.* (London), 98 (1960); (c) *J. Chem. Soc.*, 3858 (1961); (d) *Chem. Ind.* (London), 329 (1959).

(10) H. Vollman, H. Becker, M. Corell, and H. Streeck, *Ann.*, **531**, 51, 130 (1937).

(11) Some L-region oxidation to the 7,12-quinone also occurred.

(12) Some bond cleavage products also obtained.

(13) A referee has noted that the corrected redox potential correlation does not fit anthracene in nonionic solvents.[7c] If such had been the case, it would have been both surprising and probably fortuitous since the redox potentials invariably are measured in 95% ethanolic solution. With the single exception of picene,[9a] however, all the compounds correlated[6f] have been ozonized in at least 3:1 methylene chloride–methanol (sufficient to consider the solvent polar) or acetic acid. Anthracene, when ozonized in the latter solvent (ref. 7c also mentions methylene chloride–methanol), does fit the correlation.

(14) The recent suggestion[15] that ozone reacts at the K- and L-regions with the lowest localization energies, "provided that the *p*-positions are weighted by about 0.1 unit" unfortunately overlooks a most important point. Even with this additional correction, localization energies predict predominant ozone attack at the K-region, rather than the L-region, in benz[a]anthracene. In our hands, the reverse is simply true.[6d] Dean, Copeland, and McNeil have demonstrated some measure of reactivity of the K-region under conditions different from ours.[9a] However, the sensitivity of the ozone reaction to solvent,[7b,c] and temperature demand that comparison of these theoretical indices be made with the mode of predominant ozone attack of each of these unsubstituted polycyclic aromatic hydrocarbons *under identical reaction* conditions. With these necessary limitations, L-region attack predominates in benz[a]anthracene, and the indices suggested by others,[15,16] predict the reverse.

(15) A. Streitweiser, "Molecular Orbital Theory for Organic Chemists," John Wiley and Sons, Inc., New York, N. Y., 1961, p. 440.

(16) F. T. Wallenberger, *Tetrahedron Letters*, No. **95**, 5 (1959).

(17) R. Callighan and M. H. Wilt, *J. Org. Chem.*, **26**, 5212 (1961).

(18) There is considerable kinetic evidence for this. *Cf.* P. S. Bailey, *Chem. Rev.*, **58**, 958 (1958), for a summary of earlier work; T. W. Nakagawa, L. J. Andrews, and R. M. Keefer, *J. Am. Chem. Soc.*, **82**, 269 (1960).

(19) G. M. Badger, *Brit. J. Cancer*, **2**, 309 (1948).

carried out at −78° with ozone–oxygen, and ozone–nitrogen streams. Two series of experiments were made: reaction of **1** with one molar equivalent, and ozonization to saturation with 2.5 molar ozone equivalents. The resulting solution and the precipitated, unstable peroxidic mixture (**2**) defied separation and identification by chemical and physical means. Therefore, it was subjected directly to oxidative decomposition.

A number of conventional oxidants were used for decomposition of the ozonides, the most successful of which were dilute, aqueous hydrogen peroxide and freshly precipitated silver oxide. The use of the former led to the isolation of benz[*a*]anthracene-7,12 dione (**3**), 1,2-anthraquinonedicarboxylic acid (**4**), and phthalic acid (**5**). For the isolation of 1,4-dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2′-carboxylic acid (**7**), in addition to **3** and **4**, it was imperative to use the mild oxidant silver oxide, and to avoid any application of heat either to reactants or products.[20]

With increasing polarity of solvent in the series methylene chloride, 3:1 methylene chloride–methanol, and acetone, the yields of **3** increased to the extent of 10% with the maximum average results of over forty runs summarized in Table I. The extraordinary difficulty encountered in the isolation of **4** and **7** precluded any discrimination between solvent effects and the difference in work-up procedures. Further, oxidation of **1** with either 10% hydrogen peroxide or alkaline silver oxide led to a 95–97% recovery of **1**. The oxidized moiety which was separated on a Florisil column did not contain **3**, nor was it soluble in alkaline solution. It was not investigated further.

TABLE I

OZONIZATION PRODUCTS AND AVERAGE % YIELDS

Mole ratio ozone: 1	3[a]	4[a]	5[a]	7[b]	6[a]
1.0	23	6	..	14	*ca.* 2
2.5	29	15	11	8	..

[a] After hydrogen peroxide oxidation. [b] After alkaline silver oxide oxidation.

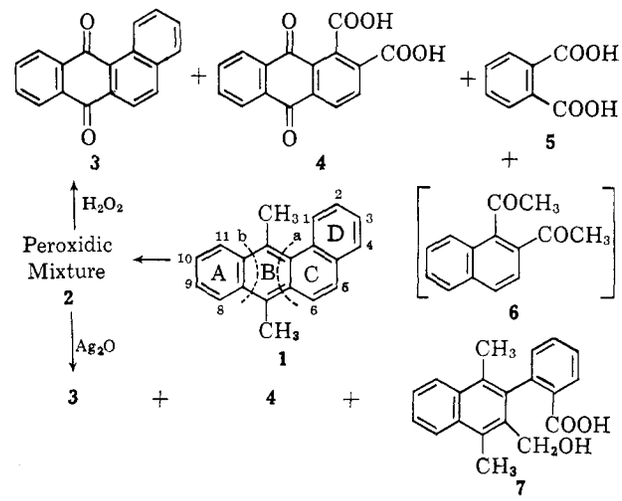
Vapor phase chromatography of original ozonolysis solution confirmed the presence of **3** emanating from the column at a column temperature of 310°.[22] The chromatogram also showed a shoulder at *ca.* 185°, approximately 5% of the 310° peak area. All attempts to collect the effluent samples from the 185° shoulder were fruitless.

However, when a filter paper impregnated with a glycine solution was pressed against the ejection port of the chromatograph, a blue coloration appeared on the filter paper at the point of contact. A blue color was also produced with aniline and *o*-phenylenediamine. No such coloration was observed with these amines for any other peaks observed in the chromatogram.

(20) These mild oxidative conditions account for the lower yields of **3** and **4** obtained with this reagent. **7** readily forms the ε-lactone, and this facile lactonization is largely responsible for the difficulties encountered in the isolation of **7**.[21]

(21) H. I. Hadler and A. C. Kryger, *J. Org. Chem.*, **25**, 1896 (1960).

(22) Addition of authentic samples of **3** to the ozonolysis solution prior to its injection in the v.p.c. column lead to an increase in the 310° peak area in proportion to the amounts added.



Riemschneider[23a] has reported the formation of a blue color in the reaction of various amino acids with compounds containing *o*-carbonyl groups, such as *o*-diacetylbenzene, *o*-diacetylcyclohexane, and *o*-dipropionylbenzene. Ozonolysis of **1** conceivably can result in four fragments which would exhibit the required *o*-carbonyl groups. Cleavage along line *a* of central ring B would yield *o*-diacetylbenzene and 1,2-naphthoquinone, while along line *b* would lead to 1,2-diacetylnaphthalene and *o*-benzoquinone. Cleavage along line *a* seems improbable due to the considerable steric hindrance of the methyl substituent on C-12 and the lateral ring D. However, *o*-benzoquinone (dec. 60–70°) and 1,2-naphthoquinone (dec. 145–147°) can be eliminated as possible causes of the 185° shoulder since both are thermally instable and decompose well below the ejection temperature. Further, an authentic sample of *o*-diacetylbenzene was desorbed from the v.p.c. column at considerably lower temperatures. Thus we believe the 185° shoulder to be 1,2-diacetylnaphthalene (**6**). Two independent approaches to the synthesis of **6** were unsuccessful.[24]

Finally, oxidation of **1** with sodium dichromate in acetic acid gave a 70% yield of **3**.

Experimental[25]

Ozonization of 7,12-Dimethylbenz[*a*]anthracene (1).—Ozone (3.5 vol. % or ozone–nitrogen) was dispersed into a solution of **1**[26] (2.0 g., 7.8 mmoles) in 300–500 ml. of methylene chloride, 3:1 methylene chloride–methanol, and acetone at −78°, until the calculated amount of ozone was absorbed. The solution ab-

(23) (a) R. Riemschneider, *Monatsh. Chem.*, **91**, 1034 (1960); (b) R. Riemschneider, *Ber.*, **92**, 1205 (1959); *Ann.*, **646**, 18 (1961); (c) R. Riemschneider, *Gazz. chim. ital.*, **81**, 479 (1951); (d) R. Riemschneider and K. Preuss, *Monatsh. Chem.*, **90**, 924 (1959).

(24) See Experimental.

(25) The ozonator used in this research was a Welsbach Corporation T-23 laboratory ozonator. The infrared spectra were run on a Perkin-Elmer Model 137 Spectracord.

Vapor phase chromatography separations were effected on an F and M Scientific Corp. Model 500 equipped with a 2-ft., silicone-gum rubber column, initial column temp., 50°, temperature programmed 6.4° per min., helium flow rate, 40 ml. per min. Microanalyses were performed by Schwarzkopf Microanalytical Laboratory, Woodside, N. Y. Melting points were determined on a Kofler micro melting point apparatus and are corrected. Boiling points are uncorrected. All solvents were Fisher Scientific Co. certified grade and were used without further treatment.

(26) Eastman 5149; disposable polyethylene plastic gloves (Handgards) were used throughout this research. The fluorescence of **1** under ultraviolet light was quite useful in its surveillance. An ever present reminder for care in handling **1** was a photograph of a cluster of papillomas initiated in a mouse by 1 μg. of **1** [V. Darchun and H. I. Hadler, *Cancer Res.*, **16**, 316 (1956)].

sorbed ozone readily up to 1.5 molar equivalents. Thereafter the absorption capacity of the solution steadily declined and became negligible at saturation after absorption of 2.5 molar ozone equivalents. Approximately 3.5–4.0 molar equivalents of ozone were added before saturation was achieved. In all experiments, ozonization was terminated after absorption of 1.0 or 2.5 (±0.1) molar ozone equivalents. The solution then was flushed with dry nitrogen to remove excess ozone. Addition of petroleum ether (30–60°) precipitated a voluminous peroxidic solid (**2**), m.p. 110–150° dec., which darkened rapidly on filtration, and exploded on heating in an open flame. Compound **2** contained active oxygen since it liberated iodine from an acetic acid solution of potassium iodide.

Oxidation of Peroxidic Mixture (2) with Aqueous Hydrogen Peroxide.—Hydrogen peroxide (10% aqueous) (70 ml.) was added to the solution of **2** and the heterogeneous mixture was then refluxed for 20 hr. with stirring. Solvents were removed *in vacuo* to leave a viscous yellow oil which was dissolved in 50 ml. of methylene chloride. This solution was extracted repeatedly with 50-ml. portions of dilute ammonium hydroxide until the alkaline extracts were colorless. The combined alkaline extracts gave solution A.

The methylene chloride layer (B) was then washed successively with water, dilute hydrochloric acid, and water, and finally dried over anhydrous sodium sulfate. Filtration followed by evaporation of the solvent (steam bath) left an oily semisolid. This material was dissolved in a minimum amount of carbon tetrachloride, deposited on a 40 × 2 cm. Florisil-packed column, and eluted with carbon tetrachloride. The carbon tetrachloride fractions were evaporated to dryness to give an oil which resisted all attempts to crystallize. This oil gave the strong violet-blue fluorescence of unchanged **1** on irradiation with ultraviolet light. Further elution with 99% benzene:1% ether led, after solvent evaporation, to a bright yellow solid. One recrystallization from methanol gave benz[*a*]anthracene-7,12-dione (**3**), identified by m.p. 169–170° (lit.[6d] m.p. 169–171°), mixture melting point, and superimposable infrared spectra with an authentic sample of **3**.

Alkaline layer A was successively extracted with methylene chloride, benzene, and ether, followed by acidification with dilute sulfuric acid. The resulting suspension was extracted continuously with ether for 24 hr. The ether extracts were dried over anhydrous sodium sulfate, filtered, and evaporated to dryness to leave a semisolid material; trituration with a small amount of chloroform produced a grey-colored solid; one recrystallization of this crude material from water gave phthalic acid (**5**) identified by m.p. 201–203°, mixture melting point, and super-imposable infrared spectra with authentic **5**.

The chloroform-soluble material was evaporated to dryness; the residue was dissolved in benzene, deposited on a Woelm's nonalkaline aluminum oxide (activity grade I) packed column, and eluted with ethyl acetate. Evaporation of the ester solvent led to crude 1,2-anthraquinonedicarboxylic acid (**4**). One recrystallization from dilute hydrochloric acid solution gave **4**, m.p. of anhydride 320–322° (lit.[6d] m.p. 320–323°).

Oxidation of Peroxidic Mixture (2) with Alkaline Silver Oxide.—A freshly prepared suspension of silver oxide (5.0 g. of silver nitrate, dissolved in 100 ml. of water to which was added 5.0 g. of sodium hydroxide in 50 ml. of water) was added to the solution of **2** and the heterogeneous mixture was shaken mechanically overnight. The resulting black precipitate was filtered and washed thoroughly with water, methylene chloride, and ether. The combined filtrates and washings were separated into two layers, organic (A), and aqueous, alkaline (B). Portion A was washed successively with water, dilute nitric acid, and water, and then dried over anhydrous sodium sulfate. Filtration, solvent evaporation, and chromatography as described in the hydrogen peroxide oxidation led to **3**.

Portion B was washed successively with methylene chloride, benzene, and ether. The aqueous dark-colored solution was cooled by addition of ice chips, and carefully acidified with dilute nitric acid. The precipitated acid mixture was extracted immediately with chloroform; the chloroform extracts were washed with water and dried over anhydrous sodium sulfate. Filtration and solvent evaporation produced a yellow semisolid which was dissolved in benzene and adsorbed on an activated silicic acid column. Elution with ether followed by evaporation of solvent gave **4**, m.p. of anhydride 318–321°, after recrystallization from dilute hydrochloric acid solution. Further column elution with ethyl acetate ultimately led to 1,4-dimethyl-3-hydroxymethyl-2-phenylnaphthalene-2′-carboxylic acid (**7**) as colorless, hairlike needles, m.p. 166.5–167.5°, after recrystallization from acetone–hexane (lit.[21] m.p. 165–165.2°); a mixture melting point with authentic **7** showed no depression and the infrared spectra were identical.[27]

Oxidation of 1 with Sodium Dichromate in Acetic Acid.—To a solution of **1** (1.0 g., 3.9 mmoles) in 20 ml. of boiling glacial acetic acid was added a solution of 3.0 g. of sodium dichromate in 10 ml. of glacial acetic acid and 2 ml. of water. The mixture was refluxed 1 hr., cooled, and poured into 100 ml. of water. The precipitated quinone was filtered, washed successively with warm water, dilute alkali, and again with water. This crude material was dissolved in benzene, adsorbed on alumina, and eluted with benzene–ether. One final recrystallization from methanol (or ethanol) gave **3**, m.p. 169–170°, in 70% yield.

Attempted Preparations of 1,2-Diacetylnaphthalene (6). From 2′-Acetonaphthone.—This synthesis was patterned after that for *o*-diacetylbenzene.[23a,b,28] 2′-Acetonaphthone (Eastman 3118) was converted in 58% yield to 2-ethylnaphthalene, b.p. 127–129° (14 mm.) [lit.[29] b.p. 127–129° (14 mm.)] *via* a modified Clemmensen reduction. Low temperature and light-insulated bromination of 2-ethylnaphthalene led in 74% yield to 1-bromo-2-ethylnaphthalene, b.p. 151–153° (7 mm.) [lit.[30] b.p. 125–126° (3 mm.)]. The Grignard of 1-bromo-2-ethylnaphthalene was converted with carbon dioxide in 60% yield to 2-ethyl-1-naphthoic acid, m.p. 117–119° (lit.[30] m.p. 118–119°). A second Grignard reaction between 2-ethyl-1-naphthoyl chloride, b.p. 158–159° (7 mm.) [lit.[30] b.p. 129–131° (2–3 mm.)] and methylmagnesium iodide led in 95% yield to 2′-ethyl-1′-acetonaphthone as a yellow oil, b.p. 158–159° (7 mm.), $\lambda_{max}^{CCl_4}$ 5.92 (s) (C=O).

Anal. Calcd. for $C_{14}H_{14}O$ (198.25): C, 84.48; H, 7.08. Found: C, 84.88; H, 6.83.

Oxidation of 2′-ethyl-1′-acetonaphthone with potassium permanganate in magnesium nitrate buffer,[23a,b] or silver permanganate in pyridine[23c] gave only a 96% recovery of unchanged 2′-ethyl-1′-acetonaphthone and trace amounts of **6**. An ethereal extract of reaction products was brought into contact with a filter paper impregnated with an aqueous solution of glycine. Oven drying the paper at 75° for 30 min. produced a light purple coloration of the wetted spots.

From 1-Vinylcyclohexane and 3-Hexene-2,5-dione.—Selenious acid oxidation of 2,4-hexanedione (K and K) gave a 20% yield of 3-hexene-2,5-dione, as faint yellow needles, m.p. 73–75° (lit.[23d] m.p. 75–79°). The tedious, reported petroleum ether extraction of the dione from the reaction mixture could be supplanted by dissolving the oil in benzene and filtering the solution through a 40 × 2 cm. Florisil-packed column. Addition of petroleum ether (60–95°) precipitated the dione in pure form.

Catalytic reduction of 1-ethynyl-1-cyclohexanol (K and K) with 2% palladized strontium carbonate led in 76% yield to 1-vinylcyclohexanol, b.p. 84–86° (30 mm.) [lit.[31] b.p. 66–68° (14 mm)]. Distillation of 1-vinylcyclohexanol over freshly fused, powdered potassium hydrogen sulfate converted it in 84% yield to 1-vinyl-1-cyclohexene b.p. 141–143° (760 mm.) [lit.[31] b.p. 143–144° (760 mm.)].

A sealed tube, Diels–Alder addition of 3-hexene-2,5-dione to 1-vinyl-1-cyclohexene (stabilized with a trace of hydroquinone) at 230° for 3 hr. was attempted. The homogeneous reaction mixture was heated to 80° in a high vacuum for 2 hr. to remove excess dione. The resulting dark brown oil, presumably 1,2,3,5,6,7,8-heptahydro-1,2-diacetylnaphthalene, was dehydrogenated over 30% palladium–charcoal in refluxing *p*-cymene for 12 hr. Removal of the catalyst by filtration and of solvent by distillation under reduced pressure left a yellow oil which could not be further distilled without extensive decomposition. A small sample of this oil when spotted onto filter paper wetted with an aqueous glycine solution produced no coloration even after heating at 75° for 3 hr.

Discussion

Compound **1** is structurally similar to its non-carcinogenic, parent hydrocarbon, benz[*a*]anthracene. Ozonization of benz[*a*]anthracene has led to **3**[6d,9a];

(27) We are grateful to Professor Hadler for a sample of **7**.
(28) F. Weygand, *Ber.*, **89**, 994 (1956).
(29) L. F. Fieser, *J. Am. Chem. Soc.*, **61**, 3218 (1939).
(30) R. C. Fuson and D. H. Chadwick, *J. Org. Chem.*, **13**, 484 (1948).
(31) P. A. Robins and J. Walker, *J. Chem. Soc.*, 646 (1952).

oxidative work-up of the ozonolysis mixture with alkaline peroxide has produced **4**,[6d] while permanganate in aqueous pyridine oxidative decomposition has led to benzo[*d*]diphenic acid.[9a] The two methyl substituents in **1**, however theoretically, should introduce two competitive effects not present in benz[*a*]anthracene.

(i) Hyperconjugation with the aromatic moiety in **1** should enhance the electron density and, consequently, ozone attack at both the L-region, and to a lesser extent, the K-region.

(ii) Increased steric hindrance to ozone attack at the L-region should lower reaction at these sites.

On the basis of only 45% of the starting material accounted for in the 1:1 mole ratio runs, and 63% in the 2.5:1 mole ratio runs, both effects seem operative (L-region attack by ozone *is decreased* in the strongly carcinogenic **1**, relative to benz[*a*]anthracene, while simultaneous K-region cleavage *is increased*). No clean separation of these competitive factors could be derived however from the present study. Also unknown is the site of attack on that portion of **1** which is unaccounted for. The observed mode of attack on **1** by ozone, however, would be expected from Pullmans' K-region theory of carcinogenesis.

The mechanism of electrophilic ozone attack of aromatic bonds, to yield cleavage products **4**, **5**, **6**, and **7**, and reactive sites, to give **3**, has been thoroughly discussed elsewhere.[6d,e,7b,d,15,16]

Tetracyclic Phenothiazines. V. Brominations and Dehydrobrominations of Some Pyrido[3,2,1-*kl*]phenothiazines[1]

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Received November 30, 1962

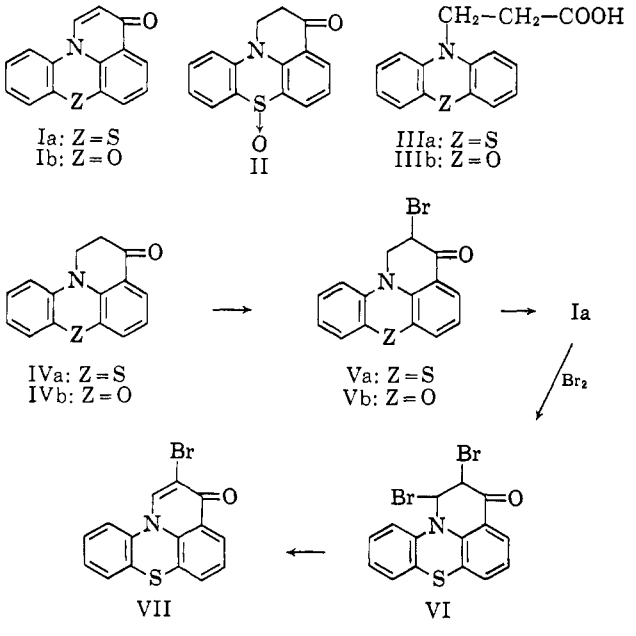
Bromination of 2,3-dihydro-3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (IVa) gave the 2-bromo derivative. This dehydrohalogenated essentially quantitatively on attempted reaction with a variety of nucleophiles. The resulting 3-keto-1*H*-pyrido[3,2,1-*kl*]phenothiazine (Ia), which has been considered "aromatic" in some respects, *adds* bromine to its dihydropyridone double bond to give VI. Compound VI dehydrohalogenates readily, *e.g.*, on solution in polar solvents. An improved synthesis of IVa is given.

A recent publication has mentioned the accidental preparation[2] and one, still more recently, the deliberate synthesis[3] of the phenothiazine Ia. The unplanned synthesis of what was presumed to be the analogous phenoxazine derivative Ib has also been reported recently.[4]

The phenothiazine, Ia, was first made by treatment of the sulfoxide, II, with hot aqueous ethanolic hydrochloric acid in an unsuccessful attempt to make a derivative of Ia chlorinated on one or both of the benzene rings. The rational preparation of Ia was by palladium-catalyzed dehydrogenation of IVa. What is probably the phenoxazine analog Ib was formed, together with the anticipated ketone IVb, by the cyclization of the phenoxazine N-propionic acid IIIb under relatively mild conditions.

Discussion of the high melting point and of the ultraviolet and infrared absorption of Ia have been given in terms of the "aromatic nature" of this substance, a point exhaustively debated in the past in connection with both 2- and 4-pyridones. However, little is known about the reactions of 2,3-dihydro-4-(1*H*)-quinolones, of which the compounds IV and V are examples[5] nor about 4-(1*H*)-quinolones such as the compound I.

We have found in the course of work directed at the preparation of amine-substituted derivatives of this ring system, that the compound Ia, whether "aromatic" or not, is the only product obtained in appreciable



amount upon treatment of the monobromo ketone Va with a variety of nucleophilic reagents. These have included sodium thiophenolate (a reagent known generally to give rapid SN2 reactions), dimethylamine (neat, in ether, in isopropyl alcohol, or in other solvents of varying polarities), anhydrous ammonia in absolute ethanol, and sodium acetate in acetic acid (a reagent which frequently gives a ratio of substitution to elimination higher than that of some other nucleophilic reagents, presumably because it leads to a reaction more nearly approximating the SN1 type). Indeed, merely keeping Va in dimethyl sulfoxide solution at room temperature for eighteen hours and subsequent dilution with water or a moderately prolonged attempt to

(1) Previous paper, M. Harfenist, *J. Org. Chem.*, **28**, 538 (1963).

(2) O. Hromatka, M. Knollmüller, and F. Sauter, *Monatsh. Chem.*, **93** 723 (1962).

(3) J. A. VanAllan, G. A. Reynolds, and R. E. Adel, *J. Org. Chem.*, **27**, 1659 (1962).

(4) P. Müller, N. P. Buu-Hoi, and R. Rips, *ibid.*, **24**, 1699 (1959).

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