Acknowledgment. We thank SERC for a studentship (to S.R.D.) and a postdoctoral research assistantship (to M.H.). We thank a referee for helpful suggestions concerning the mechanism of isomerization.

Registry No. 4, 16954-74-8; 8a, 95028-79-8; 8b, 57133-84-3; 8c, 35670-43-0; 9, 1018-78-6.

2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in Aqueous Acetic Acid, a Convenient New Reagent for the Synthesis of Aryl Ketones and Aldehydes via Benzylic Oxidation

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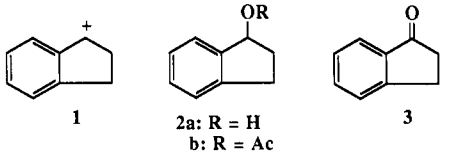
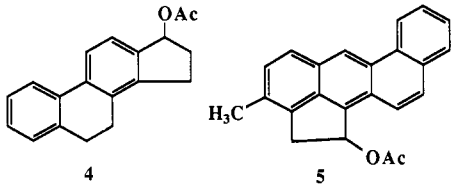
2,3-Dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in aqueous media was shown in a prior study to be a useful reagent for the oxidation of arylalkanes to yield aryl ketones and aldehydes.[1] In subsequent investigations we have found that DDQ in aqueous acetic acid is potentially of broader synthetic utility, exhibiting greater regioselectivity and affording higher yields of desired products. In Table I are summarized the results of oxidation of a large series of arylalkanes with this reagent.

The mechanism of these oxidations is thought to involve initial hydride abstraction by DDQ at a benzylic site to form a stabilized carbocation (1), which is trapped by relatively rapid reaction with acetic acid to form the acetate ester (**2b**) of the corresponding benzylic alcohol. Further oxidation of this intermediate may proceed via a second hydride abstraction at the same benzylic site or acid-catalyzed hydrolysis to yield the free alcohol **2a**, which is further oxidized to the carbonyl compound **3** by DDQ.[2,3] Under appropriate conditions the benzylic acetoxy intermediate may be isolated. Thus, when 6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene was treated with 1 equiv of DDQ in nonaqueous HOAc or when 3-methylcholanthrene was reacted with DDQ in aqueous HOAc at room temperature, the corresponding acetoxy compounds, **4** and **5**, were isolated as the principal products.

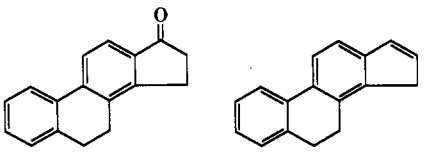


1 2a: R = H b: R = Ac 3



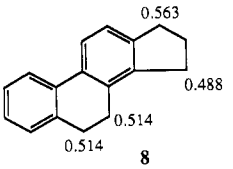
4 5

The success of this method is dependent upon the efficacy of trapping of the carbocation intermediates, the rate of which must exceed the loss of a proton to form a dehydrogenated product. Dehydrogenation is, of course, a well-known pathway for quinone oxidations.[2,4] Acetic acid appears considerably more effective than water as a trapping agent. Thus, oxidation of 6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene with DDQ in aqueous $CHCl_3$ provided a mixture of the ketone 6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthren-17-one (**6**) and the olefin 15*H*-cyclopenta[*a*]phenanthrene (**7**) in approximately equal ratio. In contrast, analogous reaction with DDQ in aqueous acetic acid furnished **6** as the sole identifiable product in 76% yield.

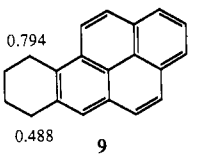


6 7

The DDQ/HOAc/H_2O reagent exhibits remarkable regioselectivity. In cases where multiple benzylic sites are present in the molecule, as in 6,7,16,17-tetrahydro-15*H*-cyclopenta[*a*]phenanthrene (**8**) the precursor of **6**, oxidative attack tends to occur selectively at a single site. Moreover, there appears to be minimal propensity for oxidation beyond the monocarbonyl stage. The site of initial hydride abstraction is that which affords the most stable carbocation intermediate predictable theoretically from the calculated β-delocalization energies.[1,5,6] Thus, in the case of **8**, the calculated values of ΔE_{deloc} for the benzylic carbocations at the C-6, -7, -15, and -17 positions are 0.514, 0.514, 0.488, and 0.563 β, respectively, and the principal product of reaction is **6** arising from oxidation at C-17.[7] Similarly, oxidation of 7,8,9,10-tetrahydrobenzo[*a*]pyrene (**9**) occurs exclusively at position C-10, which has the highest value of ΔE_{deloc} (0.794 β).



8



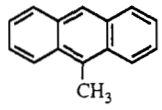
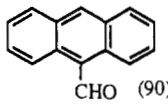
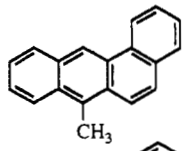
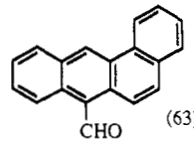
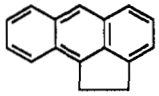
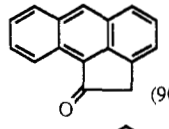
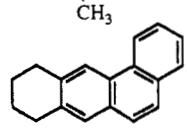
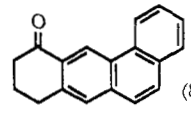
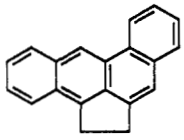
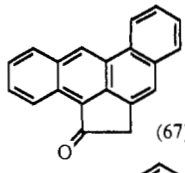
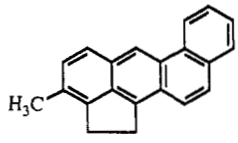
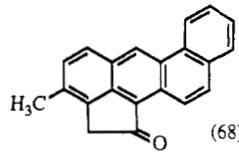
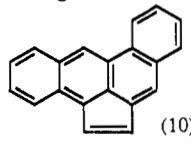
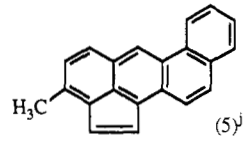
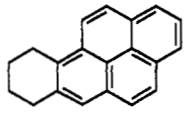
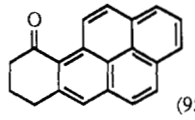
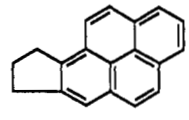
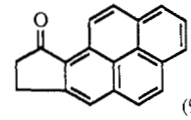
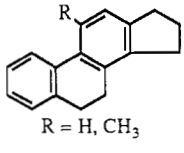
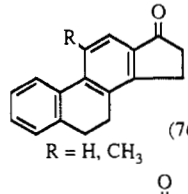
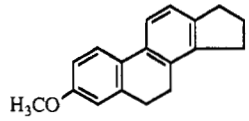
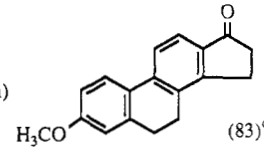
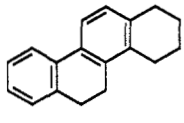
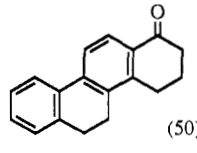
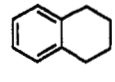
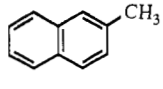
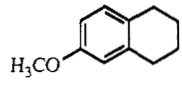
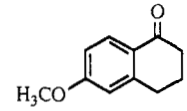
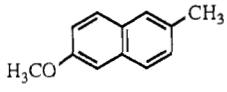
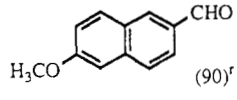
9

Methoxy and alkyl substituents at sites conjugated with the incipient carbocation intermediate markedly enhance

(1) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1983**, *48*, 749.
(2) Turner, A. B. In *Synthetic Reagents*; Pizey, J. S., Ed.; Halstead-Wiley: New York, 1977; Vol. 4, pp 193–225.
(3) Reactions conducted in the absence of added water tend to afford high ratios of benzylic acetoxy products, suggesting that hydrolysis to the free alcohol is the principal pathway in the presence of water.
(4) Fu, P. P.; Harvey, R. G. *Chem. Rev.* **1978**, *78*, 317.
(5) Fu, P. P.; Lee, H. M.; Harvey, R. G. *Tetrahedron Lett.* **1978**, 551.
(6) Fu, P. P.; Harvey, R. G.; Beland, F. A. *Tetrahedron* **1978**, *34*, 857.
(7) Calculations of β-delocalization energies are based on the perturbational method of Dewar.[8] In the case of **8**, the calculated values are for the corresponding monoalkylbiphenyls, neglecting the effect of additional alkyl substitution on carbocation stability.
(8) Dewar, M. J. S. *The Molecular Orbital Theory of Organic Compounds*: McGraw-Hill: New York, 1969; pp 304–306.
(9) Hinkel, L. E.; Ayling, E. E.; Beynon, J. H. *J. Chem. Soc.* **1936**, 344.
(10) Fieser, L. B.; Hartwell, J. L. *J. Am. Chem. Soc.* **1938**, *60*, 2555.
(11) Becker, H.; Hansen. L.; Andersson, K. *J. Org. Chem.* **1985**, *50*, 279.
(12) Fu, P. P.; Cortez, C.; Sukumaran, K. B.; Harvey, R. G. *J. Org. Chem.* **1979**, *44*, 4265.
(13) Sangaiah, R.; Gold, A.; Toney, G. E. *J. Org. Chem.* **1983**, *48*, 1632.
(14) Fieser, L. B.; Hershberg, E. G. *J. Am. Chem. Soc.* **1938**, *60*, 2542.
(15) Sims, P. *Biochem. J.* **1966**, *98*, 215.
(16) Fu, P. P.; Clark, J. D.; Huang, A. Y. *J. Chem. Res., Synop.* **1982**, 121.
(17) Lee, H.; Harvey, R. G. *J. Org. Chem.* **1982**, *47*, 4364.
(18) Jacob, G.; Cagniant, D.; Cagniant, R. *C. R. Hebd. Seances Acad. Sci., Ser. C.* **1971**, *272*, 650.
(19) Robinson, R.; Slater, S. N. *J. Chem. Soc.* **1941**, 376.
(20) Ananchenkov, S. N.; Limanov, V. Y.; Leonov, V. N.; Rzheznikov, V. N.; Torgov, I. V. *Tetrahedron* **1962**, *18*, 1355.
(21) Hudson, B. J. F. *J. Chem. Soc.* **1946**, 76.

0022-3263/88/1953-4587$01.50/0

Table I. Oxidation of Alkylaromatic Molecules with DDQ in Aqueous Acetic Acid

hydrocarbon	conditions	product (yield %)	hydrocarbon	conditions	product (yield, %)
	reflux (30 min)	 (90)[c]		reflux (2 h)	 (63)[d]
	reflux (2 h)	 (90)[e]		reflux (40 min)	 (81)[f]
	reflux (30 min)	 (67)[g]		40°C (1 h)	 (68)[i]
		 (10)[h]			 (5)[j]
	room temp (24 h)	 (95)[k]		reflux (30 min)	 (94)[l]
 R = H, CH_3	reflux (30 min)	 R = H, CH_3 (76)[m,n]		reflux (30 min)	 (83)[o]
	reflux (5 h)	 (50)[p]		reflux (24 h)	no reaction
	reflux (24 h)	no reaction		reflux (30 min)	 (65)[q]
	reflux (5 h)	 (90)[r]			

[a] General conditions: The hydrocarbon (1 mmol) was dissolved in hot acetic acid (100 mL), and 20 mL of water was added slowly, maintaining the homogeneity of the solution. As DDQ (3 mmol) was added, the solution initially became dark green. The reaction was worked up conventionally and purified by chromatography on a column of Florisil. [b] The NMR spectra of all compounds were consistent with the assigned structures and with the published spectra where available. [c] Mp 103–104 °C (lit.[9] mp 104–105 °C). [d] Mp 147–148 °C (lit.[10] mp 147.5–148 °C); NMR spectrum.[1] [e] Mp 156–157 °C (lit.[11] mp 157–168 °C). [f] Mp 117–118 °C (lit.[12] mp 116–118 °C); NMR spectrum;[11] benz[a]anthracene (10%) was obtained as a coproduct of this reaction. [g] Mp 230–231 °C (lit.[13] mp 230 °C). [h] Mp 133–134 °C (lit.[13] mp 138 °C); NMR spectrum.[13] [i] Mp >250 °C (lit.[14] mp 262–263 °C); NMR δ 2.5 (s, 3, CH_3), 3.7 (s, 2, CH_2), 7.2–9.2 (m, 8, Ar), 9.3 (s, 1, H_6). [j] Mp 196–197 °C (lit.[15] mp 194 °C); NMR δ 2.65 (s, 1, CH_3), 7.1–8.2 (m, 9, Ar and $H_{1,2}$), 8.2 (m, 1, H_7), 9.1 (s, 1, H_6). [k] Mp 175–176 °C (lit.[1] mp 175–176 °C); NMR spectrum.[16] [l] Mp 207–208 °C (lit.[17] mp 206–208 °C); NMR spectrum.[17] [m] Mp 64–65 °C (lit.[18] mp 60 °C); NMR δ 2.2 (m, 2, aliphatic), 2.7–3.2 (m, 8, benzylic), 7.1–7.4 (m, 4, Ar), 7.6 (d, 1 H_{11}), 7.7 (m, 1, H_1). [n] Oil; NMR δ 2.1 (m, 2, H_{16}), 2.6 (d, 3, CH_3), 2.8 (m, 8, benzylic), 7.0–7.8 (m, 5, Ar). [o] Mp 104–105 °C (lit.[19] 101–102 °C); NMR δ 2.1 (t, 2, H_{16}), 2.85 (m, 8, benzylic), 3.85 (s, 3, CH_3O), 6.75–7.75 (m, 5, Ar). [p] Mp 120–121 °C; NMR δ 2.2 (m, 2, H_2), 2.6–3.1 (m, 4, $H_{3,4}$), 2.7 (s, 2, $H_{5,6}$), 7.2–8.2 (m, 6, Ar); 1,2,3,4-tetrahydrochrysene (15%) and chrysene (21%) were obtained as coproducts of this reaction. [q] Mp 77–78 °C (lit.[20] 78 °C). [r] Mp 65–66 °C (lit.[21] 80–81 °C); NMR δ 3.80 (s, 3, OCH_3), 7.1 (s, 1, H_5), 7.25 (m, 1, H_7), 7.4–8.0 (m, 3, $H_{3,4,8}$), 8.2 (s, 1, H_1), 10.15 (s, 1, CHO).

the ease of these oxidations. While 2-methylnaphthalene and tetralin failed to react with DDQ/HOAc even with prolonged reaction time, 6-methoxy-2-methylnaphthalene and 6-methoxytetralin reacted readily to afford good yields of the corresponding ketonic products (Table I). Similarly, 4-methylbiphenyl failed to undergo oxidation, whereas 8, which may be considered an alkyl-substituted biphenyl, underwent smooth oxidation to yield 6.

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Registry No. 6, 115338-36-8; 8, 31301-55-0; 9, 17550-93-5; DDQ,

84-58-2; 9-methylanthracene, 779-02-2; 1,2-dihydroaceanthrylene, 641-48-5; 5,6-dihydrobenz[e]aceanthrylene, 3697-25-4; 11-methyl-6,7,16,17-tetrahydro-15H-cyclopenta[a]phenanthrene, 115338-38-0; 1,2,3,4,5,6-hexahydrochrysene, 2091-91-0; 6-methoxy-2-methylnaphthalene, 26386-94-7; 7-methylbenz[a]anthracene, 2541-69-7; 8,9,10,11-tetrahydrobenz[a]anthracene, 67064-62-4; 3-methylcholanthrene, 56-49-5; 7,8-dihydro-9H-cyclopenta[a]-pyrene, 82979-72-4; 3-methoxy-6,7,16,17-tetrahydro-15H-cyclopenta[a]phenanthrene, 115338-42-6; 6-methoxytetralin, 1730-48-9; 9-anthracenecarboxaldehyde, 642-31-9; 1,2-dihydroaceanthrylen-1-one, 51752-51-3; 5,6-dihydrobenz[e]aceanthrylen-5-one, 115482-66-1; benz[e]aceanthrylene, 199-54-2; 7,8,9,10-tetrahydrobenzo[a]pyren-10-one, 57652-65-0; 11-methyl-6,7,16,17-tetrahydro-15H-cyclopenta[a]phenanthren-17-one, 115338-39-1; 1,2,3,4,5,6-hexahydrochrysen-1-one, 115482-67-2; 6-methoxy-2-naphthalenecarboxaldehyde, 3453-33-6; 7-benz[a]anthracenecarboxaldehyde, 7505-62-6; 8,9,10,11-tetrahydrobenz[a]anthracen-11-one, 60968-15-2; 3-methylcholanthren-1-one, 3343-07-5; 3-methylbenz[j]aceanthrylene, 3343-10-0; 7,8-dihydro-9H-cyclopenta[a]pyren-9-one, 82979-73-5; 3-methoxy-6,7,15,16-tetrahydro-17H-cyclopenta[a]phenanthren-17-one, 17521-83-4; 6-methoxytetralin-1-one, 1078-19-9.

Papain-Catalyzed Synthesis of Aspartame Precursor in Biphasic System

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The synthesis of aspartame and its precursors has attracted the attention of many investigators.[1] The most interesting synthetic method is a thermolysin-catalyzed reaction that gives the products stereospecifically[2,3] However, this method has two drawbacks: (1) thermolysin is expensive and not readily available and (2) one extra equivalent of D- or L-Phe-OMe* is required to precipitate the product. In an attempt to use papain as a catalyst for the synthesis of P-L-Asp-L-Phe-OMe (P = Boc, Cbz, or Moz, abbreviations: Boc = *tert*-butyloxycarbonyl; Cbz = benzyloxycarbonyl; Moz = [(*p*-methoxybenzyl)oxy]-carbonyl; Asp = aspartic acid; Phe = phenylalanine) from P-Asp-OH and H-Phe-OMe, we found that P-L-Asp-L-Phe-OH instead of P-L-Asp-L-Phe-OMe was the only product when the reaction was carried out in McIlvaine buffer (McIlvine buffer consists of citric acid and sodium phosphate, see ref 10) because the initially formed methyl ester of the desired product was hydrolyzed by papain after the peptide bond was formed.[4] In order to avoid the hydrolysis, we used a McIlvaine/ethyl acetate biphasic system instead of a single phase and obtained P-L-Asp-L-Phe-OMe as the only product.

The procedure[5] for this biphasic reaction is to dissolve the two substrates in a minimum amount of buffer and to extract the product into a large volume of the immiscible organic solvent. In preliminary work, we found the solubility of the 1:1 mixture of P-Asp and Phe-OMe in McIlvaine buffer (pH 6.2) was higher than 0.5 M and that the pH of this solution had decreased to pH 5.5. The partition coefficient of P-Asp-Phe-OMe in 0.2 M solution (pH 5.5) and ethyl acetate is about 1 to 30 (calculated by HPLC quantitation).[6] Change of protecting groups (P = Boc, Cbz, and Moz) did not affect the partition coefficient significantly. In a typical study, 2.5 mmol each of the substrate in 6 mL of McIlvaine buffer (pH 6.2) and 95 mL of ethyl acetate was incubated at 37 °C for 72 h, and a yield of 70% was obtained for Moz-Asp-Phe-OMe. In a larger scale reaction, 20 mmol of the substrates were dissolved in 50 mL of McIlvaine buffer and 750 mL of ethyl acetate. Yields of and physical properties of the products are shown in Table I. Salt formation similar to that occurring in the thermolysin-catalyzed reaction was not observed for two reasons: (1) the weak acidity of reaction solution may not be suitable for the salt formation and (2) the product formed in the aqueous layer is extracted into the ethyl acetate layer without precipitation of the salt. Although the yield with use of Boc-L-Asp as substrate was acceptable, the best yield was obtained by using Moz-L-Asp. After separation of the organic layer, the enzyme solution was incubated again with the substrates as in the first run. The enzyme was still active but gave a lower yield (35%). Enzyme specificity was tested by reaction of the D,L substrate under the same conditions, and it was found that the P-L-Asp-L-Phe-OMe was the only product. The results are shown in Table II. The immobilized enzyme reaction was studied by adsorbing papain on Amberlite XAD-7.[7,8] After both substrates in ethyl acetate presaturated with McIlvaine buffer were passed through the column, the yield of Moz-L-Asp-L-Phe-OMe in the eluent was 45% as determined by HPLC.

Table I. Reaction of Various N-Protected L-Asp with L-Phe-OMe

substrates[a]	yield, %	product[b]	$[\alpha]^{25}_{D}$,[c] deg	mp, °C
Boc-L-Asp + L-Phe-OMe	54	Boc-L-Asp-L-Phe-OMe	−17.0	164–166
Cbz-L-Asp + L-Phe-OMe	70	Cbz-L-Asp-L-Phe-OMe	−16.0	121–123
Moz-L-Asp + L-Phe-OMe	75	Moz-L-Asp-L-Phe-OMe	−13.0	107–108

[a] Abbreviations: Boc = *tert*-butyloxycarbonyl; Cbz = benzyloxycarbonyl; Moz = [(*p*-methoxybenzyl)oxy]carbonyl. [b] The products were characterized by comparison with authentic samples (melting point and NMR and IR spectra). [c] The optical rotations were measured in methanol (*c* = 1).

Experimental Section

L-Amino acids were purchased from Kyowa Fermentation Co. Tokyo, Japan. D,L-Amino acids were obtained from Sigma. Solvents for synthesis and HPLC were from ALPS Chemicals Inc. Taipei, Taiwan. Amino acid derivatives were prepared according to the established method.[9] Papain (carica papaya 3.5 mAnson-E/mg) was from E. Merck. The McIlvaine buffer containing 0.5% mercaptoethanol was prepared according to Elving's procedure.[10] TLC was performed on silica gel G. 60 (E. Merck) precoated on a glass plate. The HPLC system consists of two Waters Model 6000 pumps, a Waters U6K valve–loop injector, a Waters Model 450 variable-wavelength UV detector, Waters Model 660 solvent programmer, and Shimadzu C-R2AX chro-

(1) (a) Pavlova, L. A.; Komarova, T. V.; Davidovich, Yu A.; Rogozhin, S. V. *Russ. Chem. Rev.* **1981**, *50*, 316. (b) Vinick, F. J.; Jung, S. *Tetrahedron Lett.* **1982**, *23*, 1315. (c) Tou, J. S.; Vineyard, B. D. *J. Org. Chem.* **1985**, *50*, 4982. (d) Fuganti, C.; Grasselli, P. *Tetrahedron Lett.* **1986**, *27*, 3191.

(2) Isowa, Y.; Ohmori, M.; Ichikawa, T.; Mori, K.; Nonaka, Y.; Kihara, K.; Oyama, K.; Satoh, H.; Nishimura, S. *Tetrahedron Lett.* **1979**, *20*, 2611.

(3) Oyama, K.; Kihara, K.; Nonaka, Y. *J. Chem. Soc., Perkin Trans. 2* **1981**, 356.

(4) Chen, S. T.; Li, K. F.; Wang, K. T. *J. Chin. Chem. Soc.*, in press.

(5) Nakanishi, K.; Kimura, Y.; Matsuno, R. *Biotechnology* **1986**, *4*, 452.

(6) Durrant, I.; Beynon, R. J.; Rodgers, P. B. *Archiv. Biochem. Biophys.* **1986**, *250*, 280.

(7) Oyama, K.; Nishimura, S.; Nonaka, Y.; Kinara, K.; Hashimoto, T. *J. Org. Chem.* **1981**, *46*, 5241.

(8) Barbas, C. F. III; Wong, C. H. *J. Chem. Soc., Chem. Commun.* **1987**, 533.

(9) Chen, S. T.; Weng, C. S.; Wang, K. T. *J. Chin. Chem. Soc.* **1987**, *34*, 117.

(10) Elving, P. J.; Markowitz, J. M.; Rosenthal, I. *Anal. Chem.* **1956**, *28*, 1179.

0022-3263/88/1953-4589$01.50/0