mixture melting point with an authentic sample showed no melting point depression.

Samples similarly irradiated in chloroform solution for 35 min and in methanol solution for 2.5 h were quantitatively converted to 4-methylanthrone.

A sample was irradiated in deuteriochloroform, and aliquots were removed at 5-min intervals. No peaks not attributable to **1** or 4-methylanthrone could be detected in any spectrum. Conversion was essentially complete after 20 min.

2-(2-Methylbenzyl)benzoic Acid. 2-(2-Methylbenzoyl)benzoic acid[16] (2.75 g, 11.45 mmol) was dissolved in 70 mL of a 10% solution of sodium hydroxide in water. Zinc dust (5.0 g, 0.077 mol) and $CuSO_4 \cdot 5H_2O$ (50 mg) were added, and the mixture was heated under reflux for 64 h. It was cooled and the liquid decanted from the solid residue, which was washed with water and 0.5 M hydrochloric acid. The combined aqueous solutions were acidified with 6 M hydrochloric acid, cooled in ice, and filtered to give a white solid which was recrystallized from ethanol to yield 2-(2-methylbenzyl)benzoic acid (2.52 g, 11.15 mol, 97%) as white prisms, mp 127-128 °C (lit.[17] mp 126-129.5 °C): ^{1}H NMR δ 2.22 (s, 3 H), 4.45 (s, 2 H), 7.2 (m, 8 H), and 8.14 (dd, J = 7, 2 Hz, 1 H).

4-Methylanthrone. 2-(2-Methylbenzyl)benzoic acid (325 mg, 153 mmol) was dissolved in 10 mL of concentrated sulfuric acid. The deep yellow solution was kept at room temperature for 5 h. It was then poured into ice, cold water was added, and the mixture was extracted with ether. The ether layer was extracted with dilute sodium hydroxide solution and with brine, dried over magnesium sulfate, and filtered. Evaporation of the solvent under vacuum left a pale yellow solid which was recrystallized from ethanol to yield 4-methylanthrone (177 mg, 0.85 mol, 56%) as yellow needles, mp 128-129 °C (lit.[10] mp 128.5-129.5 °C from ligroin).

Photoirradiation of 1 in Diethylamine Solution. A solution of ketone **1** (117 mg, 0.56 mmol) in 5 mL of diethylamine was flushed with nitrogen for 20 min. It was then cooled in an ice water bath and irradiated by a GE sun lamp for 30 min. Evaporation of diethylamine under vacuum left 135 mg of a light brown oil, which was chromatographed on 230-400 mesh silica gel, eluting with 12% ethyl acetate in hexane to yield ***N,N*-diethyl-2-(2-methylbenzyl)benzamide** (125 mg, 0.44 mmol, 79%) as a colorless oil: ^{1}H NMR δ 0.98 (t, J = 7 Hz, 3 H), 1.15 (t, J = 7 Hz, 3 H), 2.20 (s, 3 H), 2.99 (q, J = 7 Hz, 2 H), 3.49 (bq, J = 7 Hz, 2 H), 4.00 (s, 2 H), 7.15 (m, 8 H); IR (neat) 1670 cm^{-1}. Anal. Calcd for $C_{19}H_{23}NO$: C, 81.10; H, 8.24. Found: C, 79.76; H, 8.58.

***N,N*-Diethyl-2-(2-methylbenzyl)benzamide.** 2-(2-Methylbenzyl)benzoic acid (196 mg, 0.92 mmol) was dissolved in a solution containing *N,N*-dimethylformamide (1.5 g) in 2.5 mL of thionyl chloride. The solution was allowed to stand under an atmosphere of nitrogen for 20 h and excess thionyl chloride was evaporated under vacuum. The residue was dissolved in 10 mL of methylene chloride and cooled in an ice-water bath. The solution was stirred while diethylamine (5 mL) was added drop by drop. After completion of the addition of diethylamine the mixture was removed from the ice bath and stirred an additional 10 min. It was then poured into ice water and extracted with methylene chloride. The organic layer was washed with 0.5 M hydrochloric acid and then with brine, dried over sodium sulfate, and filtered; the solvent was evaporated to yield *N,N*-diethyl-2-(2-methylbenzyl)benzamide (252 mg, 0.90 mmol, 96%) as a brown oil. Its NMR and IR spectra and behavior on thin layer chromatography were identical with those of the product obtained from the photorearrangement of **1**.

Attempted Reaction of 1 with Diethylamine. A solution of **1** (106 mg) in 4 mL of diethylamine was allowed to stand at room temperature in the dark for 65 h. Evaporation of the diethylamine under vacuum left unchanged **1** (107 mg).

Photocondensation of 1 with Maleic Anhydride. A stream of nitrogen gas was bubbled through a solution of **1** (1.05 g, 5.05 mmol) and maleic anhydride (1.49 g, 15.1 mmol) in 60 mL of methylene chloride for 10 min. The reaction flask was then sealed with a serum cap, cooled in ice, and irradiated with a sun lamp for 2 h. The solvent was evaporated under vacuum to give 2.34 of of a light brown solid, which was stirred with 20 mL of methylene chloride and filtered. The residue was washed with a small amount of methylene chloride and twice recrystallized from ethyl acetate to yield **1,2-dihydro-4-hydroxy-1-(2-methylphenyl)naphthalene-2,3-dicarboxylic anhydride** (716 mg, 2.34 mmol, 46%) as a white powder, mp 219-222 °C: ^{1}H NMR δ 2.45 (s, 3 H), 3.52 (d, J = 3 Hz, 1 H, H at C-2), 4.97 (d, J = 3 Hz, H at C-1), 7.3 (m, 9 H); IR 3507 (vs), 1860 (m), 1860 (m), and 1770 (s) cm^{-1}. Anal. Calcd for $C_{19}H_{14}O_4$: C, 74.50; H, 4.61. Found: C, 74.69; H, 4.83.

Acknowledgment. We thank the donors of the Petroleum Research Fund, administered by the American Chemical Society, for a grant in support of this work.

Registry No. 1, 80716-28-5; **2**, 84945-28-8; **3**, 84945-29-9; **4a**, 80716-24-1; **5**, 80716-26-3; **5** dibromide derivative, 84945-37-9; **6**, 84945-30-2; **7**, 52103-68-1; **8** α-OH derivative, 80716-23-0; **8** β-OH derivative, 84945-31-3; **8** *cis*-dialcohol derivative, 84945-35-7; **8** *trans*-dialcohol derivative, 84945-36-8; **9** α-OCH_3 derivative, 84945-32-4; **9** β-OCH_3 derivative, 84945-33-5; **10**, 80716-25-2; **12**, 80716-27-4; **12** dibromide derivative, 84945-34-6; **13a**, 85026-70-6; **13b**, 85026-15-9; **18**, 80716-39-8; **19**, 80716-40-1; 1,3-butadiene, 106-99-0; 2-methylnaphthoquinone, 58-27-5; 1,4-naphthoquinone, 130-15-4; 10-methylanthrone, 73653-01-7; 9-methoxyanthracene, 2395-96-2; 4-methylanthrone, 80716-38-7; *N*-phenylmaleimide, 941-69-5; 2-(2-methylbenzyl)benzoic acid, 7111-77-5.

(16) Scholl, R.; Donat, J. *Chem. Ber.* **1931**, *64*, 318.
(17) Fieser, L.F.; Heymann, H. *J. Am. Chem. Soc.* **1942**, *64*, 376.

Rearrangement and Fragmentation Reactions of Blocked Aromatic Alcohols

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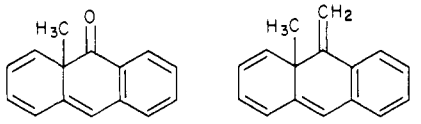
Contribution from the Department of Chemistry, University of Massachusetts, Amherst, Massachusetts 01003. *Received August 20, 1982*

Abstract: Alcohols **3** and **5**, which contain semibenzene ring systems, react unusually slowly in acidic solutions. Reaction of **3** with sulfuric acid in acetic acid gives ketone **9**, resulting from fragmentation of the central ring. Alcohol **5** under the same conditions gives a rearrangement product, 9-methylanthracene, as well as a fragmentation product. In solutions containing acetic anhydride both **3** and **5** give solely products resulting from molecular rearrangements. Factors responsible for determining the reaction products and reactivities of the starting alcohols are discussed.

In the preceding paper we reported the synthesis of ketone **1**, the first reported compound δ containing two rings which are simultaneously prevented from achieving aromaticity by the presence of a single blocking group.[1] We hoped to be able to convert **1** to the fused blocked aromatic hydrocarbon **2** by reaction with methylenetriphenylphosphorane, but our attempts failed. Only recovered **1** was obtained. Similarly, reaction of **1** with lithium trimethylsilylmethide[2] or with magnesium and diiodo-

(1) Miller, B.; Bhattacharya, A. K., preceding paper in this issue.
(2) Barton, T. J.; Hoekman, S. K. *J. Am. Chem. Soc.* **1980**, *102*, 1584.

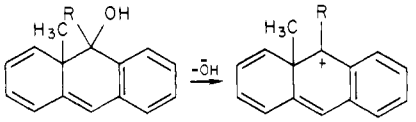
0002-7863/83/1505-3242$01.50/0



1 2

methane[3] gave no identifiable products other than recovered **1**.

These sophisticated attempts to convert the carbonyl group in **1** to a methylene group having failed, we decided to try to accomplish the conversion by a more primitive route—reaction of **1** with methyllithium and dehydration of the resulting tertiary alcohol (**3**). This process would have intrinsic chemical interest, since most methods for dehydration of **3** would involve formation



3, R = CH_3 **4**, R = CH_3
5, R = H **6**, R = H

of the intermediate carbenium ion **4**, which is identical with the arenium ion (σ complex) which might theoretically be formed by attack at a ring juncture during electrophilic methylation of 9-methylanthracene. This ion, or other ions which would result from electrophilic attack at ring junctures of polycyclic aromatic systems, have never been detected (or, to the best of our knowledge, proposed as reaction intermediates) before this work.

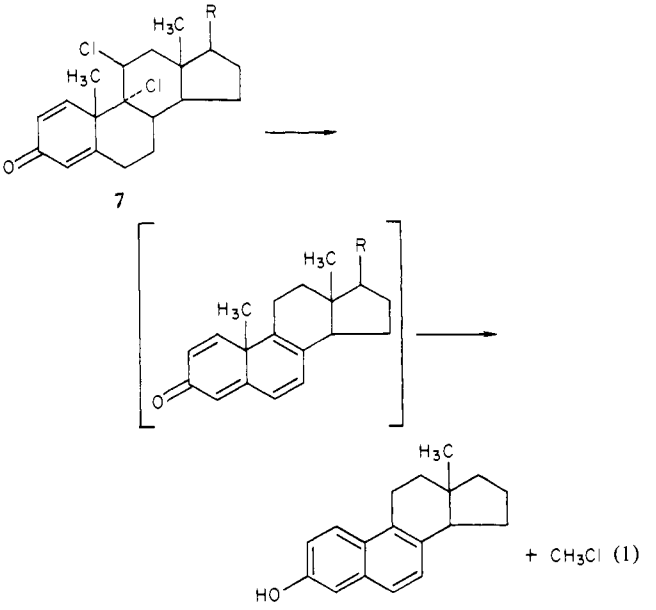
In this paper, we report on the products obtained from reaction of alcohol **3**, and its secondary analogue **5**, with acidic solutions. Although hydrocarbon **2** could not be obtained in this manner, interesting and unexpected processes did occur.

Formation of Alcohols 3 and 5

Reaction of ketone **1** with methyllithium, followed by column chromatography on silica gel, yielded the tertiary alcohol **3** in 70% yield. Inspection of the NMR spectrum of the crude product (before chromatography) showed it to be almost identical with that of pure **3**. No evidence for formation of more than one stereoisomer could be detected.

Reduction of **1** with lithium aluminum hydride similarly gave a mixture consisting principally of a single secondary alcohol. The only other product identified was anthracene, which was isolated in 0.55% yield. (VPC analysis of **1** showed that anthracene was not present before $LiAlH_4$ reduction.) Despite this very low yield, the formation of anthracene by reduction of **1** is of appreciable interest, since cleavage of methyl groups from carbon–carbon bonds at low temperatures is a very rare process.[4] (One such reaction, demethylation of the steroidal cyclohexadienone **7** in refluxing DMF,[4b] is of appreciable interest since a ketone with fused blocked aromatic rings may be an intermediate in the reaction; see eq 1.)

As yet, we have only negative evidence about the mechanism of formation of anthracene in $LiAlH_4$ reduction of **1**. Alcohol **5** does not appear to be an intermediate since further reaction of **5** with $LiAlH_4$ does not yield anthracene, nor does use of excess $LiAlH_4$ in the reduction of **1** increase the amount of anthracene formed. Since the most obvious route to anthracene was by nucleophilic demethylation of carbenium ion **4**, we attempted

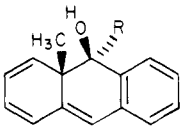


7

+ CH_3Cl (1)

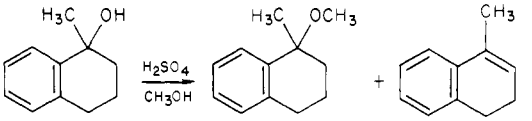
demethylation of **5** by reaction with sulfuric acid in di-*n*-butyl sulfide. No anthracene was produced.

The geometries of **3** and **5** could not be established from their spectra. It seemed likely that addition of methyl and hydride groups would occur most readily from the side of **1** anti to the angular methyl group, so that **3** would have the *trans*-dimethyl geometry and **5** the methyl and C-9 hydrogens in trans positions, as shown. This assignment, at least for **3**, was supported by the



3, R = CH_3
5, R = H

observation that both **3** and **5** were recovered unchanged after standing in 1 M solutions of hydrochloric acid in methanol for 4 h. In contrast, 1-methyl-1-tetralol (**8**) was converted to a mixture containing 45% **8**, 50% 1-methoxy-1-methyltetralin, and 5% 1-



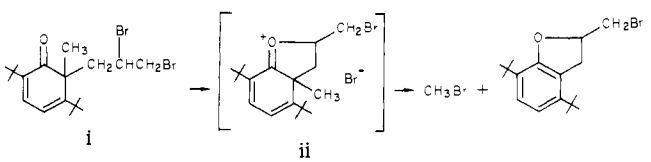
8

methyl-3,4-dihydronaphthalene after 5 min in 0.01 M hydrochloric acid in methanol. (After 5 min in 1 M HCl–MeOH solution, the product consisted of 50% 1-methoxy-1-tetralin and 50% 1-methyl-3,4-dihydronaphthalene.) Since we would have detected less than 2% of the products of methanolysis of **3**, alcohol **8** must be at least 10^5 times as reactive toward hydrochloric acid in methanol as is **3**. Similarly, 1-tetralol was converted to 1-methoxytetralin in 35% yield after 20 min in 1 M hydrochloric acid in methanol. It thus appears to be at least 10^2 times as reactive as either alcohol **5** or the tertiary alcohol **3** under these conditions.

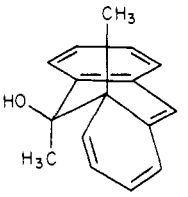
We suggest that the suprisingly low rate of methanolysis of **3** in acid confirms that **3** does indeed have the *trans*-dimethyl structure. Inspection of molecular models shows that the hydroxy group in that stereoisomer occupies a pseudoequatorial position within 15° of the plane of the aromatic ring, and essentially orthogonal to the aromatic π system, as shown. The transition state for formation of carbenium ion **4** from **3** should therefore obtain little assistance from conjugation with the aromatic ring. (A somewhat similar situation is found in 9-hydroxy-9,10-dihydroanthracenes, in which formation of very stable dihydroanthracenium carbenium ions can be inhibited by location of the leaving groups in pseudoequatorial positions.[5])

(3) Miyamo, S., et al. *Nippon Kagaku Kaishi* **1972**, 1760.

(4) (a) Demethylation of ketone i proceeds rapidly at 50–60 °C, presumably via the cyclized oxonium salt ii (Miller, B. *J. Am. Chem. Soc.* **1967**, *89*, 1685). (b) Heller, M.; Lenhard, R. H.; Bernstein, S. *Ibid.*, **1964**, *86*, 2309.



i ii

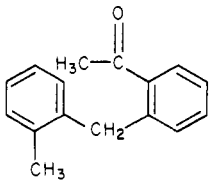


The relative unreactivity of alcohol **5** compared to 1-tetralol suggests that **5** also has the hydroxy group in the pseudoequatorial position. However, the argument is less compelling in this case, since methanolysis of the secondary alcohols may involve appreciable participation by the solvent. Such participation is likely to be hindered in **5** as compared to 1-tetralol. Assignment of the geometry shown above for **5**, therefore, depends to an appreciable extent on analogy with the geometry of **3**.

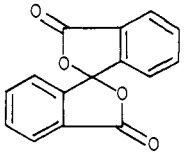
Reactions of Alcohols 3 and 5

Attempted dehydration of either **3** or **5** employing 1 mol of *p*-toluenesulfonyl chloride or thionyl chloride in pyridine resulted in recovery of the unreacted blocked aromatic alcohols, while reaction with excess *p*-toluenesulfonyl chloride under these conditions gave black, tarry products which were not investigated further.

Reaction of **3** with 0.04 M sulfuric acid in acetic acid solution at room temperature for 22 h gave, in addition to a small amount of recovered **3**, a single major product (isomeric with **3**) which, to our suprise, exhibited an aromatic carbonyl peak at 1688 cm^{-1} in its IR spectrum. Its NMR spectrum showed two methyl singlets (apparently bonded to aromatic rings or carbonyl groups) and a methylene singlet at δ 4.27, in addition to aromatic absorptions. Oxidation of the product with chromium trioxide in acetic acid converted it to 3,3′-spirobiphthalide[6] (**10**) showing the product to have substituents in ortho position on aromatic rings. This evidence was consistent with the structure 2-(2-methylbenzyl)-acetophenone (**9**) for the reaction product, and this structure was established by independent synthesis of **9** by reaction of methyllithium with 2-(2-methylbenzyl)benzoic acid.

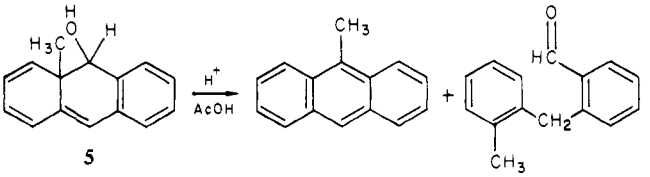


9



10

Reaction of the secondary alcohol **5** with a 0.04 M solution of sulfuric acid in acetic acid for 48 gave no recovered **5**. An approximately equimolar mixture of 9-methylanthracene and an aldehyde, isomeric with **5**, was obtained. Analogy with formation of ketone **9** from **3** suggested the structure 2-(2-methylbenzyl)-benzaldehyde (**11**) for the aldehyde, and its spectra were consistent

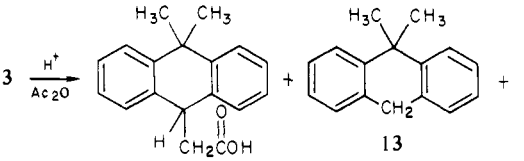


5

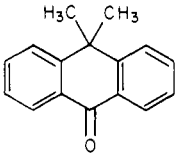
11

with this structure. Aldehyde **11** proved to be suprisingly resistant to oxidation under mild conditions and was recovered unchanged from attempted oxidation to 2-(2-methylbenzyl)benzoic acid by alkaline permanganate in water or chromium trioxide in pyridine at room temperature. Oxidation by chromium trioxide in refluxing acetic acid converted the aldehyde to the spirobiphthalide **10**, demonstrating the ortho, ortho′ locations of the substituents on the two aromatic rings.

In view of the suprising nature of the products from reactions of **3** and **5** with sulfuric acid in acetic acid solutions, we investigated the products obtained from corresponding reactions of **3** and **5** employing 0.04 M sulfuric acid in acetic anhydride solutions. Neither ketone **9** nor aldehyde **11** was obtained under these conditions. Instead, alcohol **5** yielded exclusively the "normal" rearrangement product, 9-methylanthracene. However, the principal product (45% isolated yield) from reaction of alcohol **3** with sulfuric acid in acetic anhydride was a carboxylic acid, which was assigned the structure 9-(9,10-dihydro-10,10-dimethylanthranyl)acetic acid (**12**), based on its spectra, chemical properties, and elemental analysis. In addition, smaller amounts of 9,10-dihydro-9,9-dimethylanthracene (**13**)[7] and 10,10-dimethylanthrone (**14**) were isolated. The latter two compounds were identified by comparison with authentic samples. The NMR spectrum of the crude reaction product indicated that the three products, **12**–**14**, were produced in the molar ratios 15:3:2. In



12 13



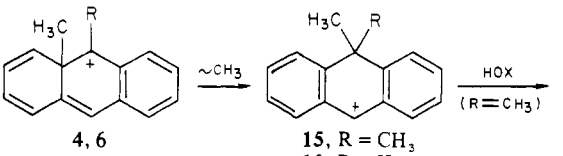
14

a second run, the product ratios were found (by NMR analysis) to be 10:6:4.

In view of the marked change in the nature of the products from reaction of alcohol **3** caused by changing the solvent from acetic acid to acetic anhydride, we examined the results of treatment of **3** with sulfuric acid in a 1:1 mixture of acetic acid and acetic anhydride. In this solvent mixture, neither ketone **9** nor acid **12**, the main products from reaction in the individual solvents, were produced. Instead **13** (53% isolated yield) and **14** (25% isolated yield) were the sole products. The spectrum of the reaction product, before separation of the components, showed the ratio **13**:**14** to be approximately 65:35.

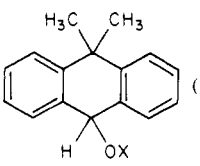
Discussion

It was expected that reactions of **3** and **5** with strong acids would initially yield carbenium ions **4** and **6**, which would each undergo rearrangement to convert the blocked aromatic systems to aromatic isomers (eq 2).



4, 6

15, R = CH_3
16, R = H

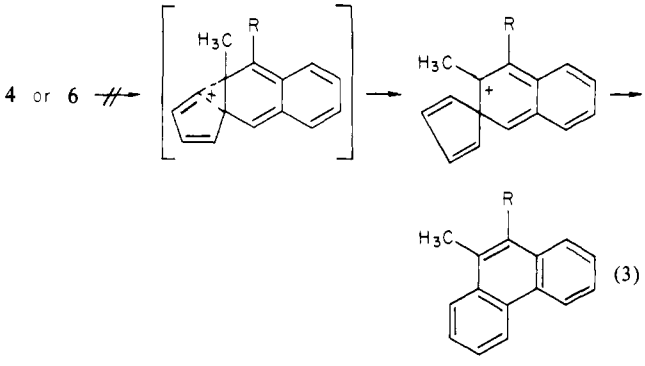


(2)

17, X = H
18, X = $COCH_3$

(5) Miller, B.; Marhevka, V. C. *Tetrahedron Lett.* **1981**, 895.
(6) Vaughan, W. R.; Andersen, M. V., Jr.; Little, R. A., Jr. *J. Am. Chem. Soc.* **1954**, *76*, 1748.
(7) Hallgarten, F. *Chem. Ber.* **1888**, *21*, 2508.

The simplest rearrangement processes would be [1,2] methyl shifts to form the 9-(9,10-dihydro)anthracenium ions **15** and **16**. The possibility that migrations of vinyl groups (to ultimately form phenanthrene derivatives) might occur could not, a priori, be excluded, but we have not been able to detect any evidence for products of vinyl group migrations. Although the vinyl group is normally a much better migrator than a methyl group in carbenium ions, its migration in **4** or **6** would not immediately convert a blocked aromatic ring to an aromatic one, as would migration of a methyl group. Furthermore, the aromaticity of the existing aromatic ring would be partially disrupted in the transition state for migration of a vinyl group in **4** or **6** (eq 3).



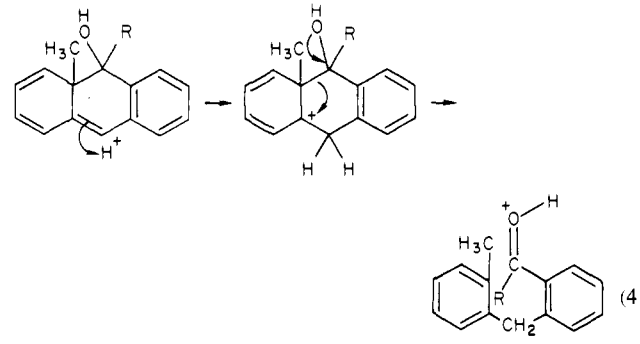
(3)

The products obtained from reactions of **3** and **5** in solutions containing acetic anhydride clearly result from methyl migrations to form ions **15** and **16**. As expected, **16** immediately loses a proton to form 9-methylanthracene, while **15** must react with nucleophiles to form dihydroanthracene derivatives. Reaction with the enol of acetic anhydride, in acetic anhydride solution, yields, after hydrolysis, acid **12**. In solutions containing acetic acid, the initial reaction product should be the acetate **18**. This product has not been detected in our work, but it has previously been shown that 10, 10-dialkyl-9,10-dihydro-9-anthracenols, such as **17**, can undergo disproportionation reactions in strong acids.[8] Thus, formation of **13** and **14** by disproportionation of **18**, is not unreasonable, although we should not have expected to obtain an excess of the reduction product, **13**, but rather have expected **13** and **14** to be formed in equal yields.

To confirm that products **12–14** would be formed from ion **15**, alcohol **17**[9] was subjected to reaction under the conditions employed for the reactions of **3**. In 0.04 M sulfuric acid in acetic acid, **17** underwent quantitative disproportionation to form **13** and **14**. The two products were obtained in precisely equimolar yields. In 1:1 acetic acid–acetic anhydride solution, **13** andd **14** were formed in a 3:2 molar ratio—essentially the same ratio of products obtained from alcohol **3** under these conditions. Apparently hydride transfer from alcohol **17** to carbenium ion **16** is rapid and is the exclusive process observed when **16** is formed in the presence of **17**. When **16** is formed by rearrangement of **3**, this process is less efficient because disproportionation of the products is rapid relative to rearrangement of **3**, so that the acetate **18** (which may be a poorer hydride donor than **17** in any case) is present in very low concentration. Reduction of **16** by some other agent therefore competes with hydride transfer from **18**. Although acetic acid and acetic anhydride are not normally very effective sources of hydride ions, we find it hard to suggest any other agents for reduction of **18**.

In acetic anhydride solution, **17** yielded **12**, **13**, and **14** in the molar ratios 8:6:4. Although it is not clear why the yield of **12** varies from run to run, it is obvious that the products from reaction of **3** and **5** with acid, with the exception of the fragmentation products **9** and **11**, can all arise via methyl migrations to form the dihydroanthracenium ions **15** and **16**.

Unlike the other products, **9** and **11** appear to be formed by protonation of **3** and **5** at C-10, followed by, or simultaneous with, fragmentation of the central ring (eq 4).



(4)

This type of fragmentation process represents a novel, though reasonable, reaction of the semibenzene ring system. Fragmentation can presumably compete with solvolysis because of the abnormally slow rates of carbenium ion formation from **3** and **5**. Formation of **9** and **11** in solutions containing acetic anhydride is probably prevented by rapid acetylation of the alcohols, which should both increase the rates of their solvolysis to form **4** and **6** and slow down fragmentation processes.

We should not overlook the very suprising observation that 9-methylanthracene is formed from reaction of the secondary alcohol **5** in acetic acid, while no evidence could be obtained for formation of products resulting from loss of a hydroxy group from the tertiary alcohol **3** under these conditions. In fact, the observation that 9-methylanthracene is obtained from **5** under conditions in which **3** is partially recovered unchanged (and no rearrangement products are formed) strongly suggests that the secondary ion, **6**, is formed more rapidly than the tertiary ion, **4**![10] (While a slow rate of methyl migration to the tertiary carbenium center in **4** could account for the absence of rearrangement products, it could not explain why **3** is recovered unchanged, rather than being converted to its acetate.)

One possible explanation for the apparently more rapid dissociation of the secondary alcohol is that conversion of the tertiary alcohol, **3**, to a conformation in which the hydroxy group occupies a pseudoaxial position is inhibited by nonbonded repulsions between the methyl group at C-9 and the two peri hydrogens at C-1 and C-8. Such repulsions would be negligible in the secondary alcohol, which could thus be more easily converted to the more reactive, though more strained, conformation with a pseudoaxial hydroxy group.

Exclusive formation of ketone **9** from **3** in acetic acid might also result from more rapid fragmentation of **3** than of **5**. This would presumably reflect the greater bond energy of a ketone carbonyl compared with that of an aldehyde, which should result in a lower energy of activation for fragmentation of **3** than for fragmentation of **5**.

Experimental Section

General. All reagents and solvents were reagent grade or were purified by standard methods before use. All ^{1}H NMR spectra were taken on a Perkin-Elmer Model R12A spectrometer in deuteriochloroform solution, using Me_4Si as an internal standard. IR spectra were recorded on a Perkin-Elmer Model 237B spectrometer. Spectra of solids were taken in mineral oil mulls, and spectra of oils were taken without solvents. Microanalyses were carried out by the University of Massachusetts Microanalytical Laboratory. Melting points and boiling points are uncorrected.

9,9a-Dihydro-9,9a-dimethyl-9-anthracenol (3). A solution of methyllithium in ether (1.3 M, 9 mL, 0.0104 mol) was added slowly to a stirred solution of 9a-hydro-9a-methyl-9-anthracenone (**1**) (0.65 g, 3.1 mmol) in 30 mL of anhydrous ether. The mixture was kept at −70 °C under an atmosphere of nitrogen until addition of metyllithium was complete, and the temperature was then allowed to rise to 0 °C for 1 h, and to 23 °C for another hour. The reaction mixture was carefully

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(9) Leute, R.; Winstein, S. *Tetrahedron Lett.* **1967**, 2475.
(10) One other instance in which a secondary carbenium ion was formed more rapidly than a tertiary carbenium ion of similar structure has been reported.[5]

poured into a mixture of ice and water and acidified with 1 M hydrochloric acid; the layers were separated. The aqueous layer was extracted with additional ether and the combined ether extracts were washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to give 0.75 g of a yellow oil. The oil was chromatographed on 230–400 mesh silica gel, eluting with a 5% solution of acetone in hexane to yield **3** (0.50 g, 2.23 mmol, 71%) as a pale yellow oil: ^{1}H NMR δ 1.18 (s, 3 H), 1.46 (s, 3 H), 1.93 (broad s, 1 H), 5.65–6.30 (m, 5 H, with a ca. 1 H singlet at 6.17), and 6.80–7.65 (m, 4 H); IR 3500 cm^{-1}. Anal. Calcd for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.61; H, 7.31.

9,9a-Dihydro-9a-methyl-9-anthracenol (5). A solution of ketone **1** (6.35 g, 0.0305 mol) in 70 mL of anhydrous ether was added dropwise over a 35-min period to a stirred suspension of lithium aluminum hydride (1.0 g, 0.0263 mol) in 180 mL of ether under a nitrogen atmosphere. The reaction mixture was stirred at room temperature for 23 h, then carefully poured into a 0.1 M solution of sulfuric acid, and the layers were separated. The aqueous layer was extracted with ether, and the combined ether extracts were washed with water and with brine, dried over sodium sulfate, and filtered; the solvent was evaporated to give 5.45 g of a viscous oil. Chromatography on silica gel, eluting with a 5% solution of acetone in hexane, yielded 60 mg of somewhat impure anthracene. (Recrystallization from hexane yielded 30 mg, 0.55%, of pure anthracene.) Further elution yielded alcohol **5** as a yellow solid, mp 62–66 °C: ^{1}H NMR δ 0.90 (s, 3 H), 2.33 (d, J = 8 Hz, 1 H), 5.03 (d, J = 8 Hz, 1 H), 5.70–6.25 (m, 4 H), 6.26 (s, 1 H), 6.93–7.73 (m, 4 H); IR 3400 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.72. Found: C, 85.54; H, 6.70.

Reaction of 3 with Sulfuric Acid in Acetic Acid. Alcohol **3** (0.47 g, 2.1 mmol) was dissolved in 20 mL of glacial acetic acid, and one drop (ca. 0.05 mL) of concentrated sulfuric acid was added. The solution was stirred in the dark at 23 °C for 13 h, and a 1-mL sample was removed, diluted with water, and extracted with ether; the organic layer was washed with sodium bicarbonate solution, dried over sodium sulfate, and filtered, and the solvent was evaporated. The ^{1}H NMR spectrum of the sample showed that 20% of **3** remained unreacted, so the sample was redissolved in the reaction solution and stirring continued for an additional 9 h. The entire reaction mixture was then worked up as described above to give 0.40 g of a viscous brown oil. Chromatography on silica gel, eluting with a 5% solution of acetone in hexane, yielded 2-(2-methylbenzyl)acetophenone (0.17 g, 0.76 mmol, 36%) (**9**) as a pale yellow oil: ^{1}H NMR δ 2.20 (s, 3 H), 2.47 (s, 3 H), 4.27 (s, 2 H), 6.75–7.60 (m, 7 H), and 7.60–7.85 (m, 1 H); IR 1688 cm^{-1}. Continued elution yielded an additional 0.055 g (ca. 12%) of somewhat less pure **9**. Finally, on elution with 8% acetone in hexane, 12 mg (3%) of recovered **3** was obtained.

Synthesis of 2-(2-Methylbenzyl)acetophenone (9). 2-(2-Methylbenzyl)benzoic acid (0.85 g, 3.76 mmol) was dissolved in 200 mL of anhydrous ether and the solution stirred at 0 °C under a nitrogen atmosphere while a solution of methyllithium in ether (1.4 M, 7 mL, 9.8 mmol) was added dropwise. The mixture was then stirred at room temperature for an additional 16 h. The solution was cooled in ice, and water was added. The layers were separated, and the ether layer was washed with sodium bicarbonate solution, dried, filtered, and evaporated to give 0.70 g of yellow oil. Chromatography on silica gel, eluting with 5% acetone in hexane, yielded 2-(2-methylbenzyl)acetophenone (0.34 g, 1.51 mmol, 40%). Anal. Calcd for $C_{16}H_{16}O$: C, 85.67; H, 7.19. Found: C, 85.91; H, 7.04. Its NMR and IR spectra were identical with those of the product obtained from reaction of **3** with sulfuric acid in acetic acid.

Chromic Acid Oxidation of 2-(2-Methylbenzyl)acetophenone. A solution of 2-(2-methylbenzyl)acetophenone (93 mg, 0.415 mmol), obtained by fragmentation of alcohol **3**, and CrO_3 (1.1 g, 11 mmol) in 70 mL of acetic acid was stirred and heated at 68-70 °C for 50 min, and then heated at reflux for an additional 80 min. The resulting green solution was poured into 1 M hydrochloric acid and extracted twice with ether. The ether extracts were washed with water, dried over sodium sulfate, filtered, and evaporated to yield 60 mg (0.237 mmol, 57%) of 3,3′-spirobiphthalide (**10**) as an off-white solid, mp 202–204 °C (lit.[6] mp 205.5–207 °C): ^{1}H NMR δ 7.15–7.50 (m, 2 H), 7.60–8.25 (m, 6 H); IR 1800 cm^{-1}.

Reaction of Alcohol 5 with Sulfuric Acid in Acetic Acid. Concentrated sulfuric acid (0.5 mL) was slowly added to a stirred solution of alcohol **5** (3.0 g, 0.0143 mol) in 200 mL of glacial acetic acid. The mixture was stirred in the dark at 23 °C for 48 h. An aliquot was then removed and worked up as described below. The remainder of the solution was allowed to stand as before for an additional 48 h. The mixture was then poured into ice water and extracted four times with hexane. The organic layer was washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to leave 2.98 g of a viscous brown oil. Its NMR spectrum was identical with that of the sample obtained after 48 h of reaction. Chromatography on silica gel, eluting with 5% ethyl acetate in hexane, yielded 0.80 g (4.2 mmol, 29%) of 9-methylanthracene, identified by comparison with a sample obtained from the Aldrich Chemical Co. Continued elution with 10% ethyl acetate in hexane yielded 2-(2-methylbenzyl)benzaldehyde (**11**) as a yellow oil (0.80 g, 3.8 mmol, 27%): ^{1}H NMR δ 2.22 (s, 3 H), 4.38 (s, 2 H), 6.75–7.60 (m, 7 H), 7.75–8.00 (m, 1 H), and 10.20 (s, 1 H); IR 1695 cm^{-1}. Anal. Calcd for $C_{15}H_{14}O$: C, 85.68; H, 6.72. Found: C, 85.45; H, 6.67.

Attempted Oxidation of 2-(2-Methylbenzyl)benzaldehyde. (a) With Potassium Permanganate. Potassium permanganate (0.3 g, 1.9 mmol) in 10 mL of water was added in small portions to a solution of 2-(2-methylbenzyl)benzaldehyde (87 mg, 0.41 mmol) and 1.8 g of potassium hydroxide in 20 mL of water to give a deep purple solution. The solution was stirred at room temperature for 1.3 h, diluted with water, and acidified with 1 M hydrochloric acid. A dilute solution of sodium bisulfite was added to decolorize the mixture, which was then twice extracted with ether. The ether layer was separated, washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to leave 78 mg of recovered 2-(2-methylbenzyl)benzaldehyde.

(b) With Chromium Trioxide in Pyridine. 2-(2-Methylbenzyl)benzaldehyde (77 mg, recovered from attempted oxidation by potassium permanganate) was dissolved in 8 mL of pyridine, and chromium trioxide (0.3 g) was added. The mixture was stirred at room temperature for 2 h, then diluted with water, and acidified with 1 M hydrochloric acid. The mixture was further worked up as described above to give 52 mg of recovered 2-(2-methylbenzyl)benzaldehyde.

Oxidation of 2-(2-Methylbenzyl)benzaldehyde by Chromium Trioxide in Acetic Acid. A solution of 2-(2-methylbenzyl)benzaldehyde (0.219 g, 1.04 mmol) and chromium trioxide (500 mg, 5 mmol) in 6 mL of glacial acetic acid was stirred and heated at reflux for 1 h. Additional chromium trioxide (0.50 g, 5 mmol) was added and refluxing continued for an additional 2 h. The reaction mixture was allowed to cool and poured into ice–water. Hydrochloric acid (1 M) was added and the mixture was extracted twice with ether. The ether extracts were washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to yield 3,3′-spirobiphthalide (96 mg, 37%), mp (from ethanol) 205–206 °C (lit.[6] mp 205.5–207 °C).

Reaction of Alcohol 3 with Sulfuric Acid in Acetic Acid and Acetic Anhydride. Concentrated sulfuric acid (0.05 mL) was added to a stirred solution of alcohol **3** (0.313 g, 1.40 mmol) in a mixture of 6 mL of acetic acid and 6 mL of acetic anhydride. The solution was stirred in the dark for 2.25 h at 23 °C. The solution was then poured into water, dilute hydrochloric acid added, and the mixture stirred at room temperature for 10 min. It was extracted with methylene chloride, and the organic layer was washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to leave 317 mg of a brown oil. Chromatography on silica gel, eluting with solutions of 3–5% ethyl acetate in hexane, yielded 9,9-dimethyl-9,10-dihydroanthracene (124 mg, 53%): ^{1}H NMR δ 1.56 (s, 6 H), 4.04 (s, 2 H), and 7.00–7.70 (m, 8 H). Further elution with 5–10% ethyl acetate in hexane yielded 10,10-dimethyl-9-anthrone (63 mg, 25%), mp 94–95 °C (lit.[7] mp 93–94 °C): ^{1}H NMR δ 1.72 (s, 6 H), 7.25–7.85 (m, 6 H), and 8.30–8.55 (m, 2 H); IR 1668 cm^{-1}.

Reaction of Alcohol 3 with Sulfuric Acid in Acetic Anhydride. Concentrated sulfuric acid (ca. 0.05 mL) was addded to a stirred solution of alcohol **3** (0.114 g, 0.51 mmol) in 4 mL of acetic anhydride, and the solution was stirred in the dark for 2 h. The reaction mixture was poured into dilute sulfuric acid and the mixture extracted three times with methylene chloride. The combined methylene chloride extracts were washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated with sodium hydroxide solution. The aqueous phase was acidified with 1 M hydrochloric acid and extracted with ether. The ether layer was washed with water, dried over sodium sulfate, and filtered; the solvent was evaporated to yield 10,10-dimethyl-9,10-dihydroanthranylacetic acid (62 mg, 0.23 mmol, 45%) as white crystals (from ether), mp 155–157 °C: ^{1}H NMR δ 1.58 (s, 3 H), 1.76 (s, 3 H), 2.75 (d, J = 7.0 Hz, 2 H), 4.66 (t, J = 7 Hz, 1 H), 7.10–7.80 (m, 8 H), and 9.6 (br s, 1 H). Anal. Calcd for $C_{18}H_{18}O_2$: C, 81.17; H, 6.81. Found: C, 81.19; H, 7.04.

The ether solution remaining after extraction with sodium hydroxide was dried and evaporated to give 27 mg of yellow oil, which was shown from its spectrum to consist of a 3:2 mixture of 9,9-dimethyl-9,10-dihydroanthracene and 10,10-dimethyl-9-anthrone.

Acid-Catalyzed Reactions of 9,10-Dihydro-10,10-dimethyl-9-anthracenol (17). (a) In Acetic Acid. Concentrated sulfuric acid (ca. 0.05 mL) was added to a solution of **17** (0.23 g) in 20 mL of glacial acetic acid. The solution was shaken and allowed to stand at room temperature for 3 h. It was then diluted with water and extracted with methylene chloride. The methylene chloride layer was washed with water and sodium bicarbonate solution, dried over magnesium sulfate, and filtered; the solvent was evaporated to leave 0.24 g of yellow oil. The ^{1}H NMR spectrum of the product showed it to consist of a 50:50 mixture of

10,10-dimethyl-9-anthrone (**14**) and 9,10-dihydro-10,10-dimethylanthracene (**13**), as determined by the relative areas of the peaks at δ 1.71 (**14**) and 1.56 (**13**). Comparison with the area of the methylene peak at δ 4.03 (**13**) confirmed the ratio.

A second run was carried out in a similar manner, except that the reaction time was extended to 24 h. The results were identical.

(b) In Acetic Acid–Acetic Anhydride. The reaction was carried out as described above, except that a mixture of 10 mL of acetic acid and 10 mL of acetic anhydride was employed as solvent. Workup was carried out as described above except that the washing with sodium bicarbonate was omitted. NMR analysis of the product showed a **13**:**14** ratio of 3:2.

(c) In Acetic Anhydride. The reaction was carried out as described above employing 0.19 g of **17** in 20 mL of acetic anhydride. The solution (after 2 h reaction time) was diluted with water and heated on a steam bath for 10 min, then extracted with methylene chloride; the methylene chloride solution was washed with water and extracted with sodium hydroxide solution. The neutral layer was washed with water, dried over magnesium sulfate, and filtered; the solvent was evaporated to give 0.10 g of yellow oil, which NMR analysis showed to consist of **13** and **14** in a ratio of 3:2. The sodium hydroxide layer was acidified with dilute hydrochloric acid and extracted with methylene chloride; the organic layer was worked up as described above to give 93 mg of acid **12**.

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Registry No. 1, 80716-28-5; **3**, 80716-32-1; **5**, 84851-99-0; **9**, 80716-33-2; **10**, 5738-26-1; **11**, 80716-34-3; **12**, 80716-37-6; **13**, 42332-94-5; **14**, 5447-86-9; **17**, 18792-73-9; methyllithium, 917-54-4; anthracene, 120-12-7; 2-(2-methylbenzyl)benzoic acid, 80716-36-5; 9-methylanthracene, 779-02-2.

Synthesis of a Cyclic Analogue of Oxidized Glutathione by an Intersite Reaction in a Swollen Polymer Network

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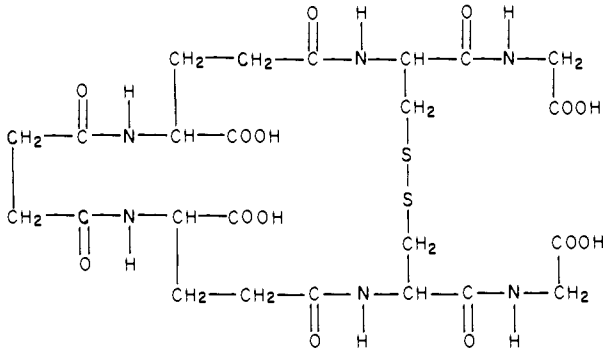
Abstract: Protected glutathione was synthesized on a 1% cross-linked copoly(styrene–divinylbenzene) resin support. Following deprotection of the α-amino groups, the chains were cross-linked in two steps. Half were acylated with succinic anhydride, with liberation of an equivalent number of carboxyl groups, which were then activated and coupled with the remaining half of the chains that still contained amines. Less than 0.5% (0.0005 mmol/g) of all the chains remained non-cross-linked. The resulting hexapeptide derivative, succinylbis[glutathione], was cleaved from the resin in HF and oxidized in air to the cyclic disulfide. The purified product was shown to be homogeneous by several chromatographic and analytical methods and to be indistinguishable from a sample prepared by solution methods. The synthesis depended on the ability to achieve a high yield of intersite reaction within the same resin bead, which required extensive flexibility of the solvent-swollen polymer matrix.

A cyclic analogue, I, of oxidized glutathione (GSSG) with



I

restricted conformation has been synthesized by solid-phase methods[1] for the purpose of studying the mechanism of action of the enzyme glutathione reductase.

This work has also provided an opportunity to examine certain aspects of the nature of the solid support used in the synthesis and in particular to answer the question of whether or not quantitative reaction between all the functional sites on the resin can be achieved. In the early period of resin-supported synthesis it was often assumed that functional sites on low-cross-linked polystyrene–divinylbenzene copolymer beads were isolated and that their reactions were analogous to reactions in solution at high dilution.[2-6] It was demonstrated, for example, that intramolecular cyclization reactions could more favorably compete with intermolecular (intersite)[7] polymerization reactions than during the same reactions carried out in solution at similar concentrations.[3] In special cases there has been evidence for long-time site isolation.[8-10] It has become more and more clear, however, that site isolation in such systems is usually a kinetic phenomenon and that site–site interaction can readily occur.[11-20] The distribution of

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