Synthetic Studies toward Quassinoids: Anomalous Results from the Metal–Ammonia Reduction of Phenanthrenone Derivatives

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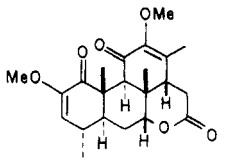
During the course of synthetic investigations in the quassinoid area, tetracyclic lactone **6** was transformed via a three-step sequence into the phenanthrenone derivative **7** in 72% overall yield. Metal–ammonia reduction of **7** provided an 84% yield of the BC cis-fused tricyclic ketone **13**. Similar reduction (Li, NH_3) of phenanthrenone **16** provided (92%) only the BC cis-fused ketone **17**. In contrast, metal–ammonia reduction of **18** afforded a 95% yield of the BC trans-fused ketone **19**. Treatment of dienedione **22**, available in 90% yield from **16** upon exposure to *p*-toluenesulfonic acid in acetone, with lithium in liquid ammonia gave rise to a 15% yield of tetracyclic diketone **24** and a 51% yield of aldol product **25**.

Our continuing interest in quassin (**1**) and related natural products [cf. quassimarin (**2**) and simalikalactone D (**3**)] has led to alternate approaches for the construction



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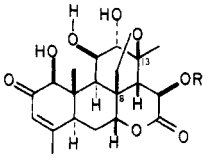


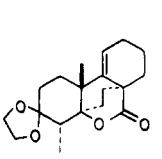
2 R = COC(OAc)(Me)Et

3 R = COCH(Me)Et

of the trans-anti-trans arrangement of the ABC ring system common to these and many other naturally occurring quassinoids.[1,2] Of particular concern was the ability to devise a short entry into quassimarin that would permit the utilization of previously developed methodology. Foremost in our minds was the desire to employ our recently disclosed method for the construction of the C(8),C(13)-epoxymethano bridge of quassimarin (cf. **4** → **5**).[1d]

4 5

With the these goals in mind, tricyclic enone **7** was prepared from tetracyclic lactone **6**, which had previously



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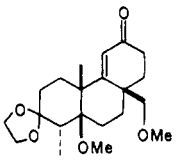

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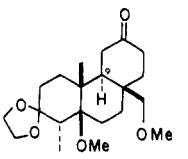
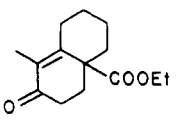


8

been described in the literature by Watt.[3] It was anticipated that metal–ammonia reduction of **7** would provide access to tricyclic ketone **8** possessing a C(9) α-oriented hydrogen. The ready availability of compound **8** renders it a viable precursor to quassimarin and related quassinoids via further elaboration employing the epoxymethano bridging reaction.[1d]

Tetracyclic lactone **6** is available in bulk quantity via a three-step sequence commencing with 2-carbethoxycyclohexanone (**9**). Condensation of **9** with ethyl vinyl ketone afforded in ca. 70% yield octalone **10**.[3] Treatment



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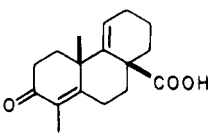

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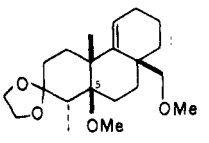
of octalone **10** with ethyl vinyl ketone/sodium ethoxide/ethanol followed by exposure to aqueous sodium hydroxide generated, in 83% yield after acidification, carboxylic acid **11**.[4] Refluxing a benzene solution of **11** containing ethylene glycol and *p*-toluenesulfonic acid gave rise (80%) to crystalline tetracyclic lactone **6**, mp 148–150 °C.[3]

The transformation of lactone **6** into the desired phenanthrenone derivative **7** proceeded smoothly. Reduction of **6** with lithium aluminum hydride in tetrahydrofuran gave rise to the corresponding diol which upon methylation (KH, MeI, THF, 18-crown-6) provided tricyclic intermediate **12** in 95% overall yield. The use of 18-crown-6 is



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(1) For previous work on quassinoids from our laboratory, see: (a) Vidari, G.; Ferriño, S.; Grieco, P. A. *J. Am. Chem. Soc.* **1984**, *106*, 3539. (b) Grieco, P. A.; Lis, R.; Ferriño, S.; Jaw, J.-Y. *J. Org. Chem.* **1984**, *49*, 2342. (c) Grieco, P. A.; Sham, H.-L.; Inanaga, J.; Kim, H.; Tuthill, P. A. *J. Chem. Soc., Chem. Commun.* **1984**, 1345. (d) Kanai, K.-i.; Zelle, R. E.; Sham, H.-L.; Grieco, P. A.; Callant, P. *J. Org. Chem.* **1984**, *49*, 3867. (e) Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C.; Williams, E. *Tetrahedron Lett.* **1981**, *22*, 1071. (f) Grieco, P. A.; Ferriño, S.; Vidari, G.; Huffman, J. C. *J. Org. Chem.* **1981**, *46*, 1022.

(2) For recent synthetic developments in the quassinoid area since 1979, see: (a) Heathcock, C. H.; Mahaim, C.; Schlecht, M. F.; Utawanit, T. *J. Org. Chem.* **1984**, *49*, 3264. (b) Batt, D. G.; Takamura, N.; Ganem, B. *J. Am. Chem. Soc.* **1984**, *106*, 3353. (c) Pariza, R. J.; Fuchs, P. L. *J. Org. Chem.* **1983**, *48*, 2306. (d) Voyle, M.; Kyler, K. S.; Arseniyadis, S.; Dunlap, N. K.; Watt, D. S. *Ibid.* **1983**, *48*, 470. (e) Voyle, M.; Dunlap, N. K.; Watt, D. S.; Anderson, O. P. *Ibid.* **1983**, *48*, 3242. (f) Fukumoto, K.; Chihiro, M.; Shiratori, Y.; Ihara, M.; Kametani, T.; Honda, T. *Tetrahedron Lett.* **1982**, *23*, 2973. (g) Kraus, G. A.; Taschner, M.; Shimagaki, M. *J. Org. Chem.* **1982**, *47*, 4271. (h) Caruso, A. J.; Polonsky, J.; Rodriguez, B. S. *Tetrahedron Lett.* **1982**, *23*, 2567. (i) Honda, T.; Murae, T.; Ohta, S.; Kurata, Y.; Kawai, H.; Takeyoshi, T.; Itai, A.; Iitaka, Y. *Chem. Lett.* **1981**, 299. (j) Dailey, O. D., Jr.; Fuchs, P. L. *J. Org. Chem.* **1980**, *45*, 216. (k) Kraus, G. A.; Taschner, M. J. *Ibid.* **1980**, *45*, 1175. (l) Pfenninger, J.; Graf, W. *Helv. Chim. Acta* **1980**, *63*, 1562. (m) Okano, M.; Lee, K.-H. *J. Org. Chem.* **1981**, *46*, 1138. (n) Kametani, T.; Chihiro, M.; Honda, T.; Fukumoto, K. *Chem. Pharm. Bull.* **1980**, *28*, 2468. (o) Mandell, L.; Lee, D. E.; Courtney, L. F. *J. Org. Chem.* **1980**, *47*, 610. (p) Stojanac, N.; Stojanac, Z.; White, P. S.; Valenta, Z. *Can. J. Chem.* **1979**, *57*, 3346.

(3) Snitman, D. L.; Himmelsbach, R. J., Watt, D. S. *J. Org. Chem.* **1978**, *43*, 4758.

(4) Snitman, D. L.; Watt, D. S. *Synth. Commun.* **1978**, *8*, 187.

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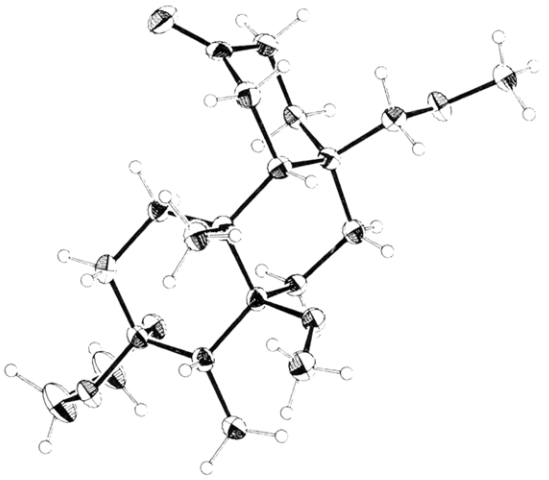
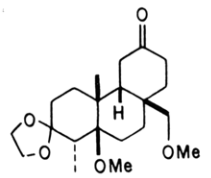


Figure 1. ORTEP view of compound **13**.

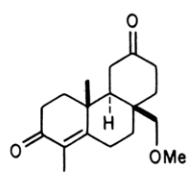
essential in order to ensure complete methylation of the hindered C(5) tertiary hydroxyl. Allylic oxidation of **12** employing Collins reagent in methylene chloride afforded after 3 h a 76% yield of enone **7**, mp 84.5–85.5 °C. Thus tricyclic enone **7** is made available via a six-step sequence starting from 2-carbethoxycyclohexanone in 30–40% overall yield.

In order to elaborate the required trans ring fusion between rings B and C of quassimarin, enone **7** was subjected to metal–ammonia reduction [Li, NH_3, *t*-BuOH, THF]. Much to our surprise, none of the anticipated tricyclic ketone **8** could be detected, instead a 84% yield of the BC cis-fused tricyclic ketone **13**, mp 154–155 °C, was isolated.



13

That the metal–ammonia reduction did not give rise to any trans-fused tricyclic ketone (cf. **8**) was made obvious by the fact that the metal–ammonia reduction product upon treatment with *p*-toluenesulfonic acid in acetone did not afford any of the known enone **14** (vide infra). The total absence of any **14** led us to speculate that the metal–ammonia reduction had proceeded contrary to expectations. The structure of the product obtained by hydrolysis of **13** was the tricyclic cis-fused ketone **15**. Unequivocal proof of structure was obtained by single-crystal X-ray analysis of the metal–ammonia reduction product **13** (Figure 1).[5]



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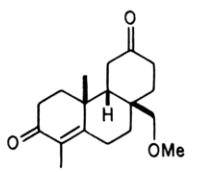

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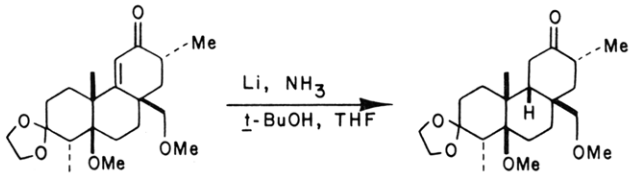
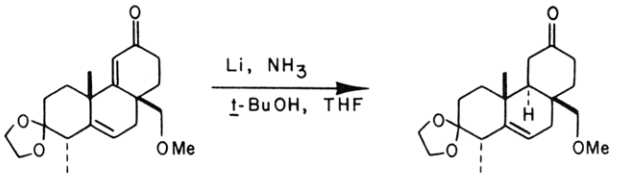
(5) Compound **13** crystallizes in space group $P2_11a$ with cell dimensions (at −160 °C) of a = 27.863 (11) Å, b = 7.972 (2) Å, c = 9.595 (2) Å, β = 117.85 (1)°; V = 1884.44 Å^3, ρ_{calcd} = 1.292 g cm^{-3} (for Z = 4). A total of 2868 reflections were measured, of which 2119 were determined to be observable, $F_o > 2.33\sigma(F_o)$. All atoms, including hydrogens, were located and refined to final residuals of $R(F)$ = 0.0392 and $R_W(F)$ = 0.0447.

In view of the above results it was not surprising to find that enone **16** (see Experimental Section), possessing a methyl group at C(13), upon reduction (Li/NH_3/*t*-BuOH/THF) provided in 92% yield ketone **17** as the sole product.

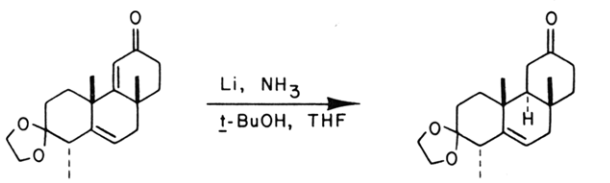


16 **17**

The formation of **13** from **7** stands in sharp contrast to what was known from similar systems. For example, it had previously been shown that tricyclic enone **18** upon reduction afforded in 95% yield crystalline tricyclic ketone **19**, mp 170.0–170.5 °C.[6] Heathcock[2a] has recently reported that reduction of enone **20** with lithium/ammonia *tert*-butyl alcohol/tetrahydrofuran provided in nearly quantitative yield the tricyclic ketone **21**.

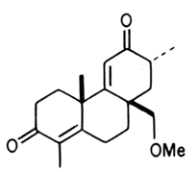


18 **19**



20 **21**

The unexpected difficulties associated with the reduction of tricyclic enone **7** led us to pursue yet another approach to the construction of an ABC intermediate possessing the tricyclic trans-anti-trans arrangement of rings. It was anticipated that hydrolysis of the ketal in **16** would yield dienedione **22** which upon reduction (Li/NH_3) might give rise to the tricyclic dione **23**. Treatment of **16** with *p*-toluenesulfonic acid in acetone provided in 90% yield crystalline dienedione **22**, mp 127.5–128.0 °C.



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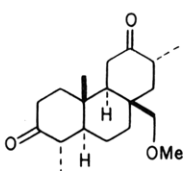
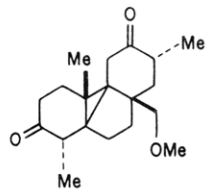


23

Reduction (Li, NH_3, *t*-BuOH, THF) of **22** did not lead to the formation of **23**. Workup provided a 15% yield of the tetracyclic diketone **24**, mp 117.5–118.0 °C,[7] and 51%

(6) Unpublished results, Dr. Paul Callant, Indiana University.

of the aldol product **25**, mp 89.0–90.0 °C. After the fact



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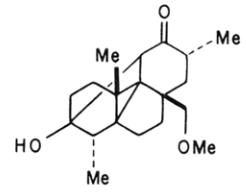
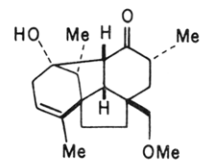


25

the formation of **24** is not totally unexpected.[8] In the absence of *tert*-butyl alcohol, the yield of **24** increased to 35% whereas the yield of the aldol product was 49%.

The structure of **25** follows from an attempted ketalization reaction. Exposure of **25** to 2-methyl-2-ethyl-1,3-dioxolane in benzene containing *p*-toluenesulfonic acid gave rise to recovered **25** (22%) and novel crystalline product **26** (25%), mp 70.0–70.5 °C, whose structure was obtained by single-crystal X-ray analysis (Figure 2).[9]



26

Efforts are still underway to find a short route to intermediates such as **23** from either **6** or **11**.

Experimental Section

Proton nuclear magnetic resonance (NMR) spectra were taken at either 360 MHz (Nicolet) or at 220 MHz (Varian) as indicated. Chemical shifts are reported in parts per million (δ) downfield from tetramethylsilane (δ 0.0). Infrared (IR) spectra were taken on a Perkin-Elmer 298 spectrophotometer in chloroform solution. Elemental analyses were performed by Galbraith Laboratories, Inc., Knoxville, TN. Melting points were obtained on a Fisher-Johns hot-stage melting point apparatus and are uncorrected. E. Merck silica gel, 70–230 mesh, was used for column chromatography and Analtech precoated silica gel plates, 0.25-mm thickness, were used for analytical thin layer chromatography (TLC). All solvents are reagent grade unless otherwise stated. "Dry" solvents were dried immediately before use. Hexamethylphosphoramide and diisopropylamine were distilled from calcium hydride. Tetrahydrofuran was distilled from sodium benzophenone ketyl. Methylene chloride was dried by passing through a column of alumina. Chromium trioxide was dried over phosphorus pentoxide. Liquid ammonia was distilled from sodium prior to use.

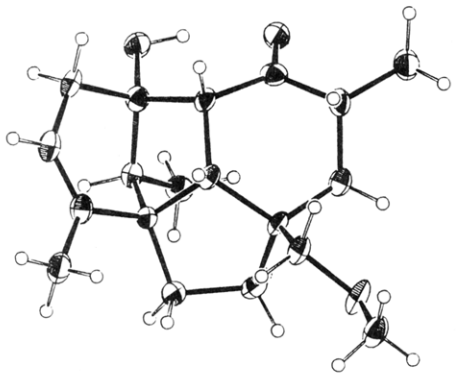


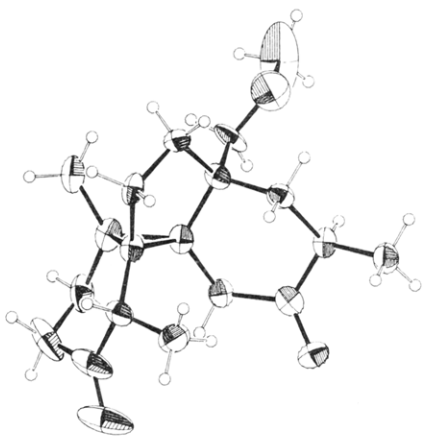
Figure 2. ORTEP view of compound **26**.

(±)-(1′α,4′aβ,8′aβ,10′aβ)-4′,4′a,7′,8′,8′a,9′,10′,10′a-Octahydro-1′,4′a-dimethyl-10′a-methoxy-8′a-(methoxymethyl)spiro[1,3-dioxolane-2,2′(1*H*)-phenanthren]-6′(3′*H*)-one (7). To 1.0 L of dry methylene chloride cooled to 0 °C were added sequentially 51.6 mL of pyridine and 32.0 g (0.32 mol) of chromium trioxide over 15 min. After 20 min, 155 g of Celite was added and stirring was continued at ambient temperature. A solution of 9.35 g (26 mmol) of olefin **12** in 100 mL of methylene chloride was added over 15 min. The reaction was quenched after 3 h by addition of 150 g of sodium hydrogen sulfate. The contents of the reaction flask were filtered through a pad of silica gel and anhydrous magnesium sulfate. The filtrate was concentrated in vacuo, leaving a brown oil which was chromatographed on 100 g of silica gel. Elution with ethyl acetate–hexane, 1:3, gave rise to 7.37 g (76%) of crystalline enone **7**, mp 84.5–85.5 °C: IR ($CHCl_3$) 1650, 1590 cm^{-1}; ^1H NMR ($CDCl_3$) (220 MHz) δ 6.07 (s, 1 H), 3.91 (m, 4 H), 3.54 (AB q, 2 H, J = 10.5 Hz, $\Delta\nu_{AB}$ = 119.5 Hz), 3.34 (s, 3 H), 3.32 (s, 3 H), 1.3–2.6 (m, 13 H), 1.27 (s, 3 H), 1.00 (d, 3 H, J = 7.0 Hz). An analytical sample was prepared by recrystallization from hexane. Anal. Calcd for $C_{21}H_{32}O_5$: C, 69.20; H, 8.85. Found: C, 69.34; H, 8.90.

(±)-(1′α,4′aβ,4′bβ,8′aβ,10′aβ)-Decahydro-1′,4′a-dimethyl-10′a-methoxy-8′a-(methoxymethyl)spiro[1,3-dioxolane-2,2′-(1′*H*)-phenanthren]-6′(3′*H*)-one (13). To 15 mL of anhydrous liquid ammonia cooled to −78 °C was added 28 mg (4.03 mmol) of lithium. After 30 min, a solution of 79 mg (0.22 mmol) of enone **7** in 3.0 mL of anhydrous tetrahydrofuran containing 204 μL (0.22 mmol) of *tert*-butyl alcohol was added at −78 °C over 30 min to the solution of lithium metal in liquid ammonia. The reaction was quenched after 30 min at −78 °C with isoprene followed by the addition of 216 mg (4.03 mmol) of ammonium chloride. The ammonia was evaporated and the residue was taken up in ethyl acetate. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent under reduced pressure afforded 75 mg (94%) of crystalline ketone **13**, mp 154–155 °C, which was pure by TLC analysis: R_f 0.56 (ethyl acetate–hexane, 1:2); IR ($CHCl_3$) 1698 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 3.90 (m, 4 H), 3.37 (AB q, 2 H, J = 9.0 Hz, $\Delta\nu_{AB}$ = 40.8 Hz), 3.36 (s, 3 H), 3.35 (s, 3 H), 2.2–2.6 (m, 8 H), 1.2–2.0 (m, 8 H), 1.10 (s, 3 H), 0.94 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from ethyl acetate. Anal. Calcd for $C_{21}H_{34}O_5$: C, 68.82; H, 9.35. Found: C, 68.59; H, 9.43.

(±)-(1′α,4′aβ,8′aβ)-4′,4′a,7′,8′,8′a,9′-Hexahydro-1′,4′a-dimethyl-8′a-(methoxymethyl)spiro[1,3-dioxolane-2,2′(1′*H*)-

(7) The structure of the tetracyclic diketone obtained follows from a single-crystal X-ray analysis of **24** (Figure i). Compound **24** crystallizes in space groups $Pbn2_1$ with cell dimensions (at −160 °C) of a = 8.989 (3) Å, b = 24.674 (10) Å, and c = 7.492 (2) Å; V = 1661.69 Å^3, ρ_{calcd} = 1.217 g cm^{-3} (for Z = 4). A total of 1400 reflections were measured, of which 994 were determined to be observable, $F_o > 2.33\sigma(F_o)$. All atoms, including hydrogens, were located and refined to final residuals of R(F) = 0.0807 and R_W(F) = 0.0823.



i. ORTEP view of Compound 24.

(8) Cf. Stork, G.; Tsuji, I. *J. Am. Chem. Soc.* **1961**, *83*, 2783. Venkataramani, P. S.; Karoglan, J. E.; Reusch, W. *Ibid.* **1971**, *93*, 269.

(9) Compound **26** crystallizes in space group $P2_12_12$, with cell dimensions of a = 7.935 (3) Å, b = 23.219 (14) Å, and c = 8.895 (3) Å; V = 1638.90 Å^3; ρ_{calcd} = 1.234 g cm^{-3} (Z = 4). A total of 2709 reflections were measured of which 1467 were determined to be observable, $F_o > 2.33\sigma(F_o)$. All atoms, including hydrogens, were located and refined to final residuals of R(F) = 0.0473 and R_W(F) = 0.0474.

phenanthren]-6′(3′*H*)-one (18). To 30 mL of dry methylene chloride containing 2.4 mL of pyridine cooled to 0 °C was added 1.5 g (15 mmol) of chromium trioxide followed by 400 mg of Celite. After 10 min, 318 mg (1.0 mmol) of (±)-(1′α,4′aβ,8′aβ)-4′,4′a,7′,8′,8′a,9′-hexahydro-1′,4′a-dimethyl-8′a-(methoxymethyl)spiro[1,3-dioxolane-2,2′(1′*H*)-phenanthrene] in 10 mL of methylene chloride was added. Upon completion of addition the ice bath was removed and stirring was continued for 13 h. The reaction was quenched by the addition of 165 mg of sodium hydrogen sulfate. The contents of the reaction flask were filtered through a pad of anhydrous magnesium sulfate and silica gel. The filtrate was concentrated in vacuo and the crude product was purified on silica gel. Elution with hexane–ethyl acetate, 4:1, provided 183 mg (55%) of crystalline enone **18**, mp 151.5–152.0 °C: IR ($CHCl_3$) 1655, 1600 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 6.13 (s, 1 H), 5.47 (m, 1 H), 3.9–4.1 (m, 4 H), 3.40 (s, 2 H), 3.30 (s, 3 H), 2.5–2.8 (m, 2 H), 2.2–2.24 (m, 3 H), 1.5–2.0 (m, 6 H), 1.26 (s, 3 H), 1.03 (d, 3 H, J = 6.8 Hz). An analytical sample was prepared by recrystallization from ether. Anal. Calcd for $C_{20}H_{28}O_4$: C, 72.26; H, 8.49. Found: C, 72.43; H, 8.60.

(±)-(1′α,4′aβ,4′bα,8′aβ)-4′,4′a,4′b,5′,7′,8′,8′a,9′-Octahydro-1′,4′a-dimethyl-8′a-(methoxymethyl)spiro[1,3-dioxolane-2,2′(1*H*)-phenanthren]-6′(3′*H*)-one (19). To 250 mL of anhydrous liquid ammonia cooled to −78 °C was added 440 mg (62.9 mmol) of lithium metal. After 15 min, a solution of 3.48 g (10.4 mmol) of enone **18** in 25 mL of anhydrous tetrahydrofuran containing 1.26 mL of *tert*-butyl alcohol was added to the solution of lithium in ammonia. Stirring was continued at −78 °C for 30 min, followed by 15 min at −33 °C. The reaction was quenched by the addition of ca. 3.0 mL of isoprene and 10.4 g of ammonium chloride. The ammonia was evaporated and the residue was taken up in 300 mL of ether. The organic layer was washed with water and dried over anhydrous magnesium sulfate. Filtration and removal of the solvent in vacuo gave crude ketone which was purified on silica gel. Elution with hexane–ether, 2:1, provided 3.3 g (95%) of crystalline tricyclic ketone, mp 170.0–170.5 °C: IR ($CHCl_3$) 1702 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 5.39 (m, 1 H), 3.8–4.1 (m, 4 H), 3.53 (AB q, 2 H, J = 9.0 Hz, $\Delta\nu_{AB}$ = 94.8 Hz), 3.33 (s, 3 H), 2.6–2.8 (m, 3 H), 2.2–2.4 (m, 4 H), 1.6–1.9 (m, 5 H), 1.2–1.4 (m, 2 H), 1.03 (s, 3 H), 1.02 (d, 3 H, J = 6.5 Hz). An analytical sample was prepared by recrystallization from *n*-heptane. Anal. Calcd for $C_{20}H_{30}O_4$: C, 71.82; H, 9.04. Found: C, 72.00; H, 9.24.

(±)-(4aβ,4bα,8aβ)-4,4a,4b,7,8,8a,9,10-Octahydro-1,4a-dimethyl-8a-(methoxymethyl)phenanthrene-2,6(3*H*,5*H*)-dione (14). A solution of 14 mg (0.04 mmol) of ketal **19** in 0.4 mL of a 1:1 mixture of tetrahydrofuran and 10% hydrochloric acid was allowed to stir at 40 °C for 2 h. The reaction was quenched with a saturated solution of sodium bicarbonate. The product was isolated by extraction with ethyl acetate. The combined organic layers were dried over anhydrous magnesium sulfate and concentrated under reduced pressure, leaving 13 mg of crude enedione. The product was purified on silica gel. Elution with hexane–ethyl acetate, 2:1, provided 12 mg (100%) of crystalline enedione **14**, mp 103–104 °C: IR ($CHCl_3$) 1705, 1660, 1610 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 3.75 (AB q, 2 H, J = 9.7 Hz, $\Delta\nu_{AB}$ = 18.9 Hz), 3.41 (s, 3 H), 2.73 (dt, 1 H, J = 3.6, 15.5 Hz), 2.2–2.6 (m, 8 H), 2.13 (ddd, 1 H, J = 3.2, 4.3, 13.3 Hz), 1.91 (m, 1 H), 1.81 (d, 3 H, J = 1.1 Hz), 1.5–1.7 (m, 2 H), 1.2 (dd, 1 H, J = 5.0, 13.3 Hz), 1.13 (s, 3 H), 1.06 (dd, 1 H, J = 2.5, 14.4 Hz). An analytical sample was prepared by recrystallization from ether. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.68; H, 8.91.

(±)-(4aβ,4bα,8aβ)-4,4a,4b,7,8,8a,9,10-Octahydro-1,4a-dimethyl-8a-(methoxymethyl)phenanthrene-2,6(3*H*,5*H*)-dione (15). A solution of 13 mg (0.04 mmol) of ketal **13** in 0.4 mL of a 1:1 mixture of tetrahydrofuran and 10% of hydrochloric acid was stirred at 40 °C for 2 h. The reaction was quenched by being poured into an ethyl acetate saturated sodium bicarbonate mixture. The product was isolated by extraction with ethyl acetate. The combined extracts were dried over anhydrous magnesium sulfate. Evaporation of the solvent left 10 mg of crude product as an oil which was purified on silica gel. Elution with hexane–ethyl acetate, 2:1, gave 8.1 mg (79%) of crystalline enedione **15**, mp 102–103 °C: IR ($CHCl_3$) 1705, 1655, 1615 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 3.38 (AB q, 2 H, J = 9.0 Hz, $\Delta\nu_{AB}$ = 34.2 Hz), 3.38 (s, 3 H), 2.2–2.7 (m, 8 H), 2.08 (m, 2 H), 1.4–2.0 (m, 5 H), 1.75 (s, 3 H), 1.32 (s, 3 H). An analytical sample was prepared by recrystallization from hexane. Anal. Calcd for $C_{18}H_{26}O_3$: C, 74.45; H, 9.03. Found: C, 74.54; H, 9.11.

(±)-(4aβ,7a,8aβ)-4,4a,8,8a,9,10-Hexahydro-8a-(methoxymethyl)-1,4a,7-trimethyl-2,6(3*H*,7*H*)-phenanthrenedione (22). To a solution of diisopropylamine (3.57 mL, 25.3 mmol) in 100 mL of dry tetrahydrofuran cooled to −78 °C was added dropwise 15 mL (22.4 mmol) of a 1.5 M solution of *n*-butyllithium in hexane. A solution of 7.1 g (19.5 mmol) of tricyclic enone **7** in 50 mL of dry tetrahydrofuran containing 4.0 mL of dry hexamethylphosphoramide was added to the cooled (−78 °C) solution of lithium diisopropylamide. After 2 h at −78 °C, 2.4 mL (39.0 mmol) of methyl iodide was added. After 15 min, the reaction was warmed to room temperature. The reaction was quenched after 1 h with a saturated ammonium chloride solution. The solvent was removed under reduced pressure. The residue was taken up in 500 mL of ether and 50 mL of a saturated sodium bicarbonate solution. The ether layer was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the filtrate under reduced pressure gave crude methylated material which was chromatographed on 100 g of silica gel. Elution with hexane–ethyl acetate, 4:1, provided 6.89 g (93%) of pure methylated ketone **16** [^1H NMR ($CDCl_3$) (220 MHz) δ 5.99 (s, 1 H), 3.7–4.0 (m, 5 H), 3.34 (s, 3 H), 3.32 (s, 3 H), 3.30 (m, 1 H), 2.3–2.6 (m, 2 H), 1.2–2.2 (m, 10 H) 1.26 (s, 3 H), 1.11 (d, 3 H, J = 6.5 Hz), 0.98 (d, 3 H, J = 6.5 Hz)] which was used directly in the next reaction.

A solution of 85 mg (0.22 mmol) of ketal **16** on 5.0 mL of acetone containing 70 mg of *p*-toluenesulfonic acid was allowed to stir for 4 h at ambient temperature. The reaction was quenched by the addition of a saturated sodium bicarbonate solution. The product was isolated by extraction with ethyl acetate. The combined organic extracts were dried over anhydrous magnesium sulfate. The filtrate was evaporated in vacuo, leaving the crude product as a crystalline material. Recrystallization from ether (2×) gave 61 mg (90%) of pure dienedione **22**, mp 127.5–128.0 °C: IR 1660, 1610, 1595 cm^{-1}; ^1H NMR ($CDCl_3$) (220 MHz) δ 6.06 (s, 1 H), 3.59 (AB q, 2 H, J = 10 Hz, $\Delta\nu_{AB}$ = 42.8 Hz), 3.36 (s, 3 H), 2.4–2.8 (m, 5 H), 2.0–2.2 (m, 4 H), 1.80 (s, 3 H), 1.3–1.5 (m, 2 H), 1.40 (s, 3 H), 1.10 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{19}H_{26}O_3$: C, 75.46; H, 8.67. Found: C, 75.67; H, 8.44.

Birch Reduction of (±)-(4aβ,7a,8aβ)-4,4a,8,8a,9,10-Hexahydro-8a-(methoxymethyl)-1,4a,7-trimethyl-2,6(3*H*,7*H*)-phenanthrenedione (22). To 100 mL of anhydrous liquid ammonia cooled to −78 °C was added 160 mg (23 mmol) of lithium. After 30 min at −78 °C, a solution of 590 mg (1.95 mmol) of dienedione **22** in 10 mL of dry tetrahydrofuran containing 368 μL (3.9 mmol) of *tert*-butyl alcohol was added over 30 min to the solution of lithium in liquid ammonia. The reaction was quenched at −78 °C after 30 min with isoprene, followed by the addition of 1.2 g of ammonium chloride. The ammonia was allowed to evaporate and the residue was taken up in ether. The ether layer was washed with brine and dried over anhydrous magnesium sulfate. Evaporation of the filtrate in vacuo gave a crude mixture of products. Purification on 20 g of silica gel employing hexane–ethyl acetate, 5:1, gave in order of elution 304 mg (51%) of crystalline aldol **25**, mp 89–90 °C [R_f 0.70 (hexane–ethyl acetate, 2:1); IR ($CHCl_3$) 3400, 1690 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 3.56 (AB q, 2 H, J = 9.4 Hz, $\Delta\nu_{AB}$ = 113.7 Hz), 3.39 (s, 3 H), 2.87 (m, 1 H), 1.5–2.2 (m, 12 H), 1.43 (t, 1 H, J = 13.7 Hz), 1.22 (s, 3 H), 0.98 (d, 3 H, J = 6.1 Hz), 0.90 (d, 3 H, J = 7.2 Hz). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 75.04; H, 9.33.] and 91 mg (15%) of crystalline dione **24**, mp 117.5–118.0 °C [R_f 0.50; IR ($CHCl_3$) 1710 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 3.58 (AB, q, 2 H, J = 9.4 Hz, $\Delta\nu_{AB}$ = 117.6 Hz), 3.37 (s, 3 H), 2.67 (m, 1 H), 2.4–2.6 (m, 3 H), 2.0–2.2 (m, 3 H), 1.7–2.0 (m, 4 H), 1.2–1.6 (m, 3 H), 1.44 (s, 3 H), 1.10 (d, 3 H, J = 6.5 Hz), 0.99 (d, 3 H, J = 7.0 Hz). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.83; H, 9.42.].

Acid-Catalyzed Rearrangement of Aldol 25. To a solution of 300 mg (0.77 mmol) of aldol **25** in 5.0 mL of benzene containing 30 mg of *p*-toluenesulfonic acid was added 114 mg (0.98 mmol) of 2-methyl-2-ethyl-1,3-dioxolane. The reaction was heated at 60 °C. After 3 h, the reaction was quenched by the addition of solid sodium bicarbonate (123 mg). After filtration and removal

of the solvent in vacuo, the crude product was purified by HPLC (μ-Porasil, 15% ethyl acetate in hexane). There was obtained 65.5 mg 22% of recovered aldol and 74 mg (25%) of crystalline ketone **26**, mp 70.0–70.5 °C: R_f 0.63 (hexane–ethyl acetate, 2:1); IR ($CHCl_3$) 3400, 1682 cm^{-1}; ^1H NMR ($CDCl_3$) (360 MHz) δ 6.71 (s, 1 H), 5.10 (br s, 1 H), 3.37 (s, 3 H), 3.27 (AB q, 2 H, J = 8.7 Hz, $\Delta\nu_{AB}$ = 38.4 Hz), 2.60 (m, 1 H), 2.58 (AB q, 2 H, J = 10.8 Hz, $\Delta\nu_{AB}$ = 78.3 Hz), 1.5–2.5 (m, 9 H), 1.68 (d, 3 H, J = 1.4 Hz), 6.99 (d, 3 H, J = 6.5 Hz), 0.82 (d, 3 H, J = 6.5 Hz). Anal. Calcd for $C_{19}H_{28}O_3$: C, 74.96; H, 9.27. Found: C, 74.85; H, 9.14.

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Hydrolysis of *N*-(Pivaloyloxy)-*p*-acetotoluidide: N–O Bond Cleavage Reactions of a Model Proximate Carcinogen

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The hydrolysis reactions of *N*-(pivaloyloxy)-*p*-acetotoluidide (**1a**), a model for the carcinogenic metabolites of polycyclic aromatic amides, were investigated by a combination of UV spectroscopy, product analyses, and HPLC methods at 70 °C over the pH range 2.0–8.0. Under these conditions **1a** undergoes exclusive N–O bond cleavage to yield products characteristic of processes involving nitrenium ion pairs. In many ways the reactions of **1a** in aqueous solution parallel those of the analogous sulfuric acid ester, **1b**. However, two unique products, 3-(pivaloyloxy)-4-methylacetanilide (**2b**) and 4-acetotoluidide (**9**), which have no analogues in the reactions of **1b** under these conditions, were isolated. The first-order rate constant for the decomposition of **1a**, which is independent of pH and buffer composition, is (380 ± 60)-fold less than the corresponding rate constant for **1b** under the same conditions. The characteristics of the hydrolysis reaction of **1a** are considerably different from those of the *N*-acetoxy-*N*-arylacetamides which undergo a considerable amount of acyl transfer under similar conditions. These results indicate that pivalic acid esters may be more appropriate models for the proximate carcinogens derived from *N*-hydroxy-*N*-arylacetamides than are the acetic acid esters if, indeed, nitrenium ions are the ultimate carcinogens.

Sulfuric acid esters appear to be important carcinogenic metabolites of polycyclic *N*-aryl-*N*-hydroxyamides.[1,2] The chemistry of a series of *N*-(sulfonatooxy)acetanilides, which are monocyclic analogues of the polycyclic sulfuric acid esters, has been the subject of a number of investigations in this laboratory.[3] In aqueous solution these compounds decompose via heterolytic N–O bond cleavage to yield tight nitrenium ion–sulfate ion pairs which undergo internal return to yield rearrangement products, and solvent-separated ion pairs which are attacked by external nucleophiles or reducing agents.[3] The closely related methanesulfonic acid esters of the *N*-hydroxyacetanilides, investigated by Gassman and Granrud, behave in a similar fashion.[4]

Carboxylic acid esters of the *N*-hydroxyacetanilides are also of interest since they present the opportunity to investigate the effect of the leaving group on the chemistry of ester derivatives of *N*-hydroxy amides. In addition, carboxylic acid esters apparently are also important carcinogenic metabolites of certain *N*-aryl-*N*-hydroxy amides.[1] *N*-acetoxy-*N*-arylacetamides have been used as model proximate carcinogens in a large number of in vivo and in vitro studies,[1,5] and a number of studies involving the solution chemistry of *N*-acetoxy-*N*-arylacetamides have appeared.[6,7] However, these acetic acid esters undergo facile acyl transfer reactions[6e,7b] which complicate the investigation of the chemistry of the N–O bond in such compounds.

Accordingly, we have synthesized and investigated the aqueous solution chemistry of *N*-(pivaloyloxy)-*p*-acetotoluidide (**1a**). The bulky pivalic acid ester was chosen so that the acyl transfer side reaction would be suppressed.

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