(s, 1.09, ArH).

Reaction of (1-Methoxy-2,4,6-trideuterio-3-phenyl)cadmium Reagent with Acetyl Chloride. To the Grignard reagent, prepared from 0.24 g (0.10 mol) of magnesium and 1.90 g of 2,4,6-trideuterio-3-bromoanisole in a total of 25 mL of dry ether, which had been heated at reflux for 60 min and stirred at room temperature for 30 min, was added 0.91 g (0.005 mol) of cadmium chloride. Stirring at room temperature was continued for 90 min; then 0.78 g (0.010 mol) of acetyl chloride in 25 mL of dry ether was added, and the mixture was stirred for 60 min. The usual workup with 10% HCl gave 1.5 g of crude oil. GC separation yielded pure *m*- (**2a**) and *p*-methoxyacetophenones (**2b**). **2a:** NMR δ 2.56 (s, 3, CH_3CO), 3.81 (s, 3, CH_3O), and 7.26 (s, 1.19, ArH); the MS indicated 66.1% d_3, 28.2% d_2, and 4.2% d_1. **2b:** NMR δ 2.43 (s, 3, CH_3CO), 3.77 (s, 3, CH_3O), and 7.77 (s, 1.0, ArH); the MS indicated 39.2% d_3, 46.7% d_2, and 11.0% d_1.

DCl/D_2O Quenching of the Reaction Mixture from *m*-Dianisylcadmium and Acetyl Chloride. The reaction mixture, prepared exactly as above except from unlabeled *m*-bromoanisole, was decomposed with 2.0 g (0.020 mol, 2.0 mL) of 20% DCl in D_2O (Aldrich), which was added via a drybag-filled syringe. After the mixture had been stirred for 90 min, it was worked up in the usual way, as described earlier, to afford 2.1 g of oil, which was separated by GC. **2a:** NMR δ 2.43 (s, 0.6, CH_3CO), 3.76 (s, 3, CH_3O), and 6.70–7.40 (m, 4, ArH). **2b:** NMR δ 2.43 (s, 0.5, CH_3CO), 3.80 (s, 3, CH_3O), and 7.25 (midpoint) (AB quartet, lower doublet at δ 7.8, 1.6; upper doublet at δ 6.8, 2.0; ArH, J = 9 Hz). Some starting *m*-bromoanisole recovered by GC showed no evidence of ring deuteration: NMR δ 3.58 (s, 3, CH_3O) and 6.45–6.91 (m, 4, ArH).

Acknowledgment. We are grateful to the University of New Hampshire for a Summer Fellowship to J.G.S.

Registry No.—**1a,** 68758-02-1; **1b,** 68758-03-2; **1c,** 55142-69-3; **1d,** 68758-04-3; **1e,** 68758-05-4; **9,** 68758-06-5; cadmium chloride, 10108-64-2; *m*-bromothioanisole, 33733-73-2; *m*-bromotoluene, 591-17-3; *m*-bromofluorobenzene, 1073-06-9; *m*-bromotrifluoromethylbenzene, 401-78-5; di-*o*-anisylcadmium, 68758-07-6; *o*-bromoanisole, 578-57-4; *o*-methoxyacetophenone, 579-74-8; 2,4,6-trideuterio-3-bromoanisole, 68758-08-7; *m*-bromoanisole, 2398-37-0; phenyl cyanurate, 1919-48-8.

References and Notes

(1) Taken in part from the Ph.D. Dissertation of James G. Shelnut, 1978.
(2) L. H. Klemm, R. Mann, and C. D. Lind, *J. Org. Chem.*, **23,** 349 (1958).
(3) W. G. Dauben and J. W. Collette, *J. Am. Chem. Soc.*, **81,** 967 (1959).
(4) J. Walravens and R. H. Martin, *Bull. Soc. Chim. Belg.*, **69,** 165 (1960).
(5) J. Cason, *Chem. Rev.*, **40,** 15 (1947).
(6) D. A. Shirley, *Org. React.*, **8,** 28 (1954).
(7) It had already been shown that the *m*-tolylcadmium reagent afforded only meta product with acetyl chloride: W. G. Dauben and K. A. Seagebarth, *J. Am. Chem. Soc.*, **73,** 1853 (1951).
(8) To our knowledge, this is the first instance of a reaction of an organic cyanate with a cadmium reagent.
(9) T.-L. Ho, *Chem. Rev.*, **75,** 1 (1975).
(10) H. C. Brown and Y. Okamoto, *J. Am. Chem. Soc.*, **80,** 4979 (1958).
(11) The CH_3CO hydrogens did exchange with deuterium during this experiment, as was the case in control reactions with *m*- and *p*-methoxyacetophenones.
(12) "Sadtler Standard Spectra", Sadtler Laboratories, Philadelphia, Pa.
(13) H. Gilman and F. Schulze, *J. Am. Chem. Soc.*, **47,** 2002 (1925).
(14) W. A. Bonner, *J. Am. Chem. Soc.*, **72,** 4270 (1950).
(15) E. Grigat and R. Putter, *Chem. Ber.*, **97,** 3012 (1964).
(16) A. W. Hoffmann, *Ber.*, **3,** 275 (1870).
(17) F. G. Bordwell and H. M. Anderson, *J. Am. Chem. Soc.*, **75,** 6021 (1953).
(18) O. L. Brady and J. N. E. Day, *J. Chem. Soc.*, 114 (1934).
(19) W. G. Brown, A. H. Widiger, and N. J. Letang, *J. Am. Chem. Soc.*, **61,** 2597 (1939).
(20) K. Fukui, H. Kitano, T. Osaka, Y. Inamoto, and H. Shirai, *Nippon Kagaku Zasshi*, **79,** 1120 (1958); *Chem. Abstr.*, **54,** 5519c (1960).
(21) J. H. Simons and E. O. Ramler, *J. Am. Chem. Soc.*, **65,** 391 (1943).
(22) W. J. Humphlett, M. J. Weiss, and C. R. Hauser, *J. Am. Chem. Soc.*, **70,** 4020 (1948).

Preparation of Derivatives of 8-, 9-, 10-, and 11-Hydroxybenz[*a*]anthracene-7,12-diones, Benz[*a*]anthracenes, and 7,12-Dimethylbenz[*a*]anthracenes[1]

Wayne B. Manning,* Gary M. Muschik, and Joseph E. Tomaszewski

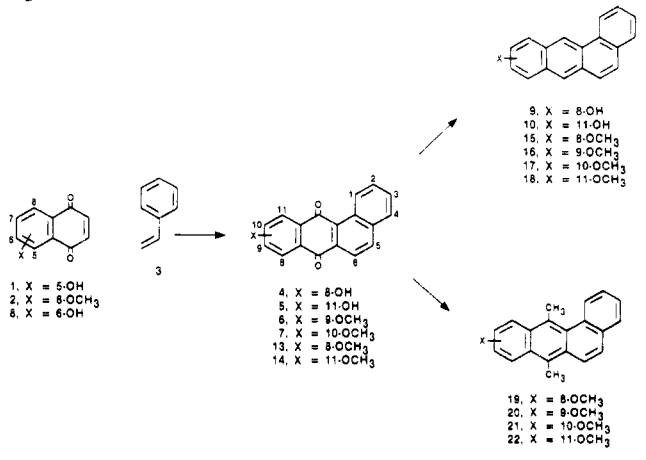
Chemical Carcinogenesis Program, NCI Frederick Cancer Research Center, Frederick, Maryland 21701

Received August 10, 1978

Methoxy- and hydroxybenz[*a*]anthracene-7,12-diones substituted at the 8, 9, 10, and 11 positions have been prepared by reaction of 5- and 6-substituted-1,4-naphthoquinones with styrene (**3**). The methoxy diones were reduced to the corresponding benz[*a*]anthracenes by either a zinc/pyridine/acetic acid reagent or aluminum tricyclohexaoxide in refluxing cyclohexanol. These diones also were converted to the respective 7,12-dimethylbenz[*a*]anthracenes by the classical Grignard method. Spectral data and certain limitations of the method are discussed.

Current investigations concerning the carcinogenicity of 7,12-dimethylbenz[*a*]anthracene (DMBA) have led to postulations that oxidative metabolism of the angular benzene ring[2] and/or the 8-, 9-, 10-, and 11-ring[3] convert DMBA to its ultimate carcinogenic form. To test aspects of the latter hypothesis by using possible metabolic products, a facile synthesis of the 8-, 9-, 10-, and 11-hydroxy derivatives of DMBA was desirable.

Morreal and Alks[4] prepared the 8-, 10-, and 11-methoxy derivatives of DMBA via a multi-step synthesis involving initial reaction of naphthylmagnesium bromide with the appropriate methoxyphthalic anhydrides. Pataki and Ballick[5] prepared the 9- and 10-hydroxy DMBA's via a similar sequence of reactions. In both instances Friedel-Crafts reactions were used to construct the carboskeleton from substituted naphthalenes and benzenes. More recently, Newman and Kumar[6] and Newman et al.[7] prepared methoxy and hydroxy DMBA's substituted in the 1, 2, 3, 4, 6, 9, and 10 positions. These synthetic pathways consisted of reactions of various organometallics with assorted carbonyl compounds followed



0022-3263/79/1944-0699$01.00/0

by cyclization reactions. In contrast, Wunderly and Weber[8] utilized the 2 + 4 cycloaddition reactions of 1,4-phenanthraquinone and 1-methoxy-1,3-cyclohexadiene to form ultimately 8- and 11- methoxybenz[*a*]anthracene-7,12-diones, which are expected precursors of the corresponding DMBA's using well-established methods.[9,10]

We wish to report the use of 2 + 4 cycloadditions of 5-hydroxy-1,4-naphthoquinone (**1**) and 6-methoxy-1,4-naphthoquinone (**2**) to styrene (**3**) to form mixtures of 8-hydroxybenz[*a*]anthracene-7,12-dione (**4**) and 11-hydroxybenz[*a*]anthracene-7,12-dione (**5**) and 9-methoxybenz[*a*]anthracene-7,12-dione (**6**) and 10-methoxybenz[*a*]anthracene-7,12-dione (**7**). After methylation of **4** and **5**, these diones were converted to the DMBA's via the procedure of Sandin and Fieser[10] and were converted to the respective benz[*a*]anthracenes using either a variation of the method of Traxler[11] or the method of Ahmed et al.[12] This cycloaddition method therefore furnishes in one step the substituted intermediate 7,12-diones which can be separated and purified at this stage for subsequent conversion to the respective benz[*a*]anthracenes and DMBA's.

Results and Discussion

The success of the Diels–Alder cycloaddition of substituted styrenes to 1,4-naphthoquinone in preparing 1-, 2-, 3-, and 4-halo-substituted benz[*a*]anthracene-7,12-diones (BAD's)[13] and 1-, 2-, 3-, and 4-methoxy BAD's[14] prompted the use of the reaction of 5- and 6-substituted naphthoquinones with styrene to synthesize BAD's substituted at the 8, 9, 10, and 11 positions.

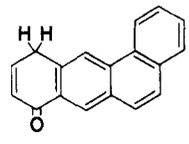
The reaction of **1** and excess styrene in the presence of chloranil yielded a combination of **4** and **5** in 74% overall yield with **5** predominating by a three to one margin. Reaction times were decreased, and yields increased, by use of catalytic amounts of trichloroacetic acid as suggested by the work of Wasserman.[15]

The method of Teuber and Gotz[16] was used to prepare 6-hydroxy-1,4-naphthoquinone (**8**) from 1,7-dihydroxynaphthalene. However, after a toluene solution of **8**, **3**, and chloranil was heated for 8 days at 100 °C, neither 9- nor 10-hydroxybenz[*a*]anthracene-7,12-dione was found. The failure of **8** to cycloadd to styrene to form substituted benz[*a*]anthracene-7,12-diones under the same conditions that were used to generate **4** and **5** could have been attributed to the poor solubility of **8** in toluene.

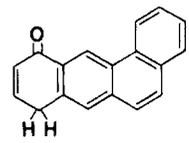
To increase the solubility of the 6-substituted 1,4-naphthoquinone in toluene, **8** was methylated by methyl iodide using freshly precipitated silver oxide in chloroform according to Garden and Thomson.[17] Reaction of the resulting 6-methoxy-1,4-naphthoquinone (**2**) with excess **3** in the presence of chloranil produced **6** and **7** in a two to three ratio in 58% overall yield.

The mixtures of **4** and **5** and **6** and **7** were separated on silica gel using an increasing gradient of benzene in hexane. The isomers **6** and **7** also were isolated preparatively by a Waters 500/Prep liquid chromatograph using toluene as eluting solvent and using the recycle mode to rechromatograph mixed fractions.

Mixed results were obtained in attempted conversions of the substituted BAD's to the respective isomers of benz[*a*]anthracene (BA). The use of zinc powder in a refluxing pyridine–acetic acid solution to produce **9** and **10** led to formation of a mixture of products which included compounds having molecular ions in the mass spectra at *m/e* 246 and 248. This was consistent with reduction to dihydro and tetrahydro derivatives. An explanation for this behavior could be the isomerization of **4** and **5** to the corresponding keto forms **11** and **12** which are further reduced to dihydro and tetrahydro products. Similar intermediates have been postulated in the



11



12

reductions of anthraquinones to anthracenes.[11] To eliminate this possibility, **4** and **5** were methylated with methyl iodide/silver oxide in chloroform to form 8-methoxybenz[*a*]anthracene-7,12-dione (**13**) and 11-methoxybenz[*a*]anthracene-7,12-dione (**14**).

Use of aluminum tricyclohexaoxide in refluxing cyclohexanol to reduce the methoxy BAD's to the respective BA's (**15–18**) succeeded with **6** and **7** (65 and 84%, respectively), but led to low yields and complex product mixtures with **13** and **14** as assayed by analytical and preparative TLC. These complex mixtures were not characterized further.

The 8-, 9-, and 11-methoxybenz[*a*]anthracenes were prepared by refluxing a pyridine/acetic acid solution of the respective BAD's with zinc, modifying the method of Traxler.[11] The BA's were produced in yields of 45–90% by this method. Reaction times varied from 8 h for the 9-methoxy isomer to 20 h for the preparation of **15**. The dihydro and tetrahydro products were not observed.

The preparation of 8-, 9-, and 10-methoxy DMBA's (**19**, **20**, and **21**) from the diones according to the general method of Sandin and Fieser[10] afforded the expected products in 45, 51, and 54% yields, respectively. When this procedure was applied to **14**, however, a complex product mixture resulted from which a minor component (~5% yield) was isolated whose melting point and mass spectrum were consistent with the expected 11-methoxy DMBA (**22**). Under our conditions this preparation does not appear to be the method of choice for synthesizing **22**. The conversion of these methoxy DMBA's to the corresponding hydroxy DMBA's has been reported elsewhere[4,5] and is not reported here. The general instability observed for these DMBA phenols does suggest, however, that generation of these phenols should occur immediately prior to use.

Because the synthetic route produces mixtures of the diones, it is imperative to be able to distinguish the isomers formed. Although the UV spectra of the 8-, 9-, 10-, and 11-substituted BAD's possessed similar general absorption curves, the infrared spectral region of 1000–700 cm^{-1} and the proton magnetic resonance spectra were clearly different and useful in distinguishing the various dione isomers. Whereas **6** exhibited absorptions at 839 and 774 cm^{-1} in its IR spectrum, **7** did not absorb at these energies but rather at 855, 765, and 759 cm^{-1}. Compound **4** could be easily differentiated from **5** by its C–O absorption at 1270 cm^{-1} vs. 1295 cm^{-1} for the C–O stretch of **5** and by the different intensities of the quinone carbonyl absorptions at about 1660 and 1625 cm^{-1}. The ^1H NMR spectra revealed the clearest differences in the resonance signals observed for the 1-proton.[18] This resonance signal in the spectrum of **4** was centered at δ 9.68 vs. 9.80 in the spectrum of **5**.

In contrast to the diones, the methoxybenz[*a*]anthracenes each possessed a UV absorption curve markedly different from the others. The four major absorptions in the 260–300-nm range found in the spectrum of **18** were replaced by three in the spectrum of **15** while the one major band at 287 nm in the spectrum of **16** was replaced by two weaker absorptions at 278 and 287 nm in **17**. Compounds **16** and **17** could easily be distinguished from **15** and **18** by their low-extinction bands at 300–310 nm.

The ^1H NMR spectra of the benz[*a*]anthracenes were the most useful for the corroboration of assignment of methoxyl substitution in the isomers **15** and **18**. The resonance signal

for the 7-proton occurring at 8.23 ppm in benz[a]anthracene[19] shifted to 8.79 ppm in **15** while the 12-proton singlet occurring at 9.03 ppm in benz[a]anthracene shifted only slightly to 9.12 ppm. In the spectrum of **18**, the shift in the 7-proton was slight (8.23 to 8.32 ppm) while the 12-proton shifted markedly (9.03 to 9.63). The changes in these proton signals were less pronounced with **16** and **17** with a general upfield shift of from 0.03 to 0.15 ppm for each signal.

Although much of the spectral data itself suggested the assignments of isomers, the proper identities of the various diones were firmly established by their conversion to the known methoxy DMBA's. With the exception of compound **22** the methoxy D ring DMBA's have been prepared by a general method in moderate yields from the intermediate diones, which, themselves, have been prepared in as few as two steps. Since the means are available for preparative separation of the dione isomers,[20] we believe the overall synthetic technique has abbreviated previous preparative pathways.

Experimental Section

General Methods. All temperatures are reported uncorrected. Melting points were determined on a Fisher-Johns hot-stage apparatus. Mass spectra were taken on a Finnigan 3300 mass spectrometer equipped with a Finnigan 6000 MS data system. A Cary 17 UV–vis spectrophotometer was used for the UV spectra, all taken in 95% EtOH. Proton magnetic resonance spectra were taken on a Varian XL-100 spectrometer using $CDCl_3$ (0.5% Me_4Si) or CCl_4 (Me_4Si) as solvents while the IR spectra were obtained on a Perkin-Elmer 467 spectrophotometer as KBr pellets. Elemental analyses were performed by Galbraith Laboratories, Knoxville, Tenn. or on a Perkin-Elmer Model 240 elemental analyzer. All column chromatography was conducted using Silicar CC-7 (Mallinckrodt). The 5-hydroxy-1,4-naphthoquinone, the styrene, and the 1,7-dihydroxynaphthalene were obtained from Aldrich.

8-Hydroxybenz[a]anthracene-7,12-dione (4) and 11-Hydroxybenz[a]anthracene-7-12-dione (5). To a mixture of 1.2 g (6.9 mmol) of 5-hydroxy-1,4-napthoquinone (**1**), 1.1 g (4.5 mmol) of chloranil, and 30 mg of trichloroacetic acid in 30 mL of toluene was added 3.0 g (29 mmol) of **3**. The mixture was heated in an oil bath at 95–100 °C for 8 days or until TLC analysis on Silica Gel GF plates showed little or no 5-hydroxy-1,4-naphthoquinone. Supplemental quantities of chloranil (0.5 g, 2 mmol) and **3** (2.0 g, 19 mmol) were added after about 4 days.

Column chromatography of the tarry product using hexane then a gradient of benzene/hexane (0–20%) revealed two red-orange bands. The first band yielded 0.30 g (16%) of **4**: mp 195–196 °C; IR 3420 cm^{-1} (OH), 1661 (C=O), 1630 (C=O), 1590, 1460, 1380, 1270, 1239, 788, 751, and 700; UV max 210 nm (log ϵ 4.65), 231 (4.51), 283 (4.57), 308 (3.77), 360 (3.67), 405 (3.92); MS *m/e* (rel intensity) 274 (M^+, 100.0), 273 (16.6), 246 (22.4), 245 (10.5), 218 (27.2), 190 (11.8), 189 (56.7), 188 (9.7), 187 (10.5), 163 (13.3), 137 (7.6), 127 (5.4), 126 (8.7). Anal. Calcd for $C_{18}H_{10}O_3$: C, 78.82; H, 3.68. Found: C, 78.57; H, 3.66.

The second band from the column yielded 1.1 g (58%) of **5**: mp 213–214.5 °C; IR 3420 (OH), 1662 (C=O), 1629 (C=O), 1585, 1460, 1380, 1295, 1223, 1208, 855, 831, and 751 cm^{-1}; UV max 213 nm (log ϵ 4.80), 233 (4.66), 287 (4.67), 310 (3.82), 367 (3.80), 409 (3.94), 425 (3.99), 450 (3.93); MS *m/e* (rel intensity) 274 (M^+, 100), 273 (18.8), 246 (18.8), 245 (21.9), 218 (24.4), 190 (15.1), 189 (74.0), 188 (11.1), 187 (13.0), 163 (14.3), 137 (14.6), 127 (5.2), 126 (5.9). Anal. Calcd for $C_{18}H_{10}O_3$: C, 78.82; H, 3.68. Found: C, 78.71; H, 3.54.

9-Methoxybenz[a]anthracene-7,12-dione (6) and 10-Methoxybenz[a]anthracene-7,12-dione (7). The reaction was conducted as above using 230 mg (1.23 mmol) of 6-methoxy-1,4-naphthoquinone (**2**), 615 mg (2.5 mmol) of chloranil, 20 mg of trichloroacetic acid, 520 mg (5.0 mmol) of **3**, and 10 mL of toluene. The reaction time was extended to 17 days and no supplemental additions of chloranil or **3** were made.

Column chromatography using hexane then a slow gradient of benzene/hexane (0–20%) yielded 80 mg (23%) of **6**: mp 169.5–171 °C in the first fraction; IR 1665 (C=O), 1597, 1308, 1240, 887, 839, 822, 774, and 761 cm^{-1}; UV max 217 nm (log ϵ 4.47), 256 (sh) (4.14), 278 (4.43), 288 (4.63), 399 (3.81); MS *m/e* (rel intensity) 288 (M^+, 100), 289 (23.7), 260 (17.9), 249 (10.3), 244 (16.7), 243 (7.1), 217 (15.4), 202 (9.0), 201 (7.7), 200 (10.3), 189 (70.5), 163 (14.1). Anal. Calcd for $C_{19}H_{12}O_3$: C, 79.16; H, 4.20. Found: C, 79.01; H, 5.35. The second band yielded 123 mg (35%) (**7**), mp 174.5–176 °C (lit.[7] mp 171.5–172.0 °C).

8-Methoxybenz[a]anthracene-7,12-dione (13). Methyl iodide (1.5 mL) was added to a mixture of **4** (200 mg, 0.69 mmol) and freshly prepared silver oxide (1.5 g) in 12 mL of chloroform. The mixture was stirred at room temperature overnight. TLC analysis then revealed the absence of reactant dione. The mixture was filtered and the filtrate passed through a short Silicar column using chloroform as eluting solvent to yield 196 mg (94%) of **14**, mp 189–190 °C. (lit.[8] mp 184–185 °C).

11-Methoxybenz[a]anthracene-7,12-dione (14). By the same procedure as above 230 mg of **5** yielded 218 mg (90%) of **15**, mp 200.5–202 °C (lit.[8] mp 195 °C).

8-Methoxybenz[a]anthracene (15). A solution of 100 mg (0.35 mmol) of **13** in 4 mL of pyridine was heated briefly in an oil bath at 100 °C. Excess zinc powder (0.5 g) was added and the mixture was stirred. Three milliliters of 80% aqueous acetic acid was then added and the mixture refluxed for 20 h, during which time 2-mL aliquots of 80% aqueous acetic acid were added each hour for the first 4 h. The mixture was filtered and the filtrate reduced to dryness under vacuum. The remaining material was chromatographed on a short column of Silicar CC-7 using benzene to yield 55 mg (61%) of **16**: mp 182–184 °C; IR 1260, 900, 891, 790, 755, and 741 cm^{-1}; UV max 231 nm (log ϵ 4.25) 269 (4.29), 28C (4.40), 291 (4.34), 319 (3.29), 335 (3.42), 350 (3.48), 370 (3.33), and 384 (3.05); MS *m/e* (rel intensity) 258 (M^+, 75.9), 243 (33.6), 226 (5.8), 216 (22.8), 215 (100), 214 (9.6), 213 (26.7). Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.18; H, 5.59.

11-Methoxy[a]anthracene (18). By the above procedure (9 h reflux), 130 mg (0.45 mmol) of **14** yielded 77 mg (66%) of **18**: mp 128–129 °C; IR 1381, 1351, 1243, 1110, 1091, 889, and 750 cm^{-1}; UV max 231 (log ϵ 4.24), 261 (4.27), 271 (4.25), 282 (4.37), 294 (4.37), 319 (3.33), 335 (3.44), 352 (3.46), 370 (3.25), 382 (3.00); MS *m/e* (rel intensity) 258 (M^+, 91.3), 243 (21.0), 229 (5.5), 226 (6.6), 216 (19.4), 215 (100), 214 (6.8), 313 (21.5). Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.49; H, 5.47.

9-Methoxybenz[a]anthracene (16). By the above procedure (8 h reflux), 35 mg (0.12 mmol) of **6** yielded 21 mg (67%) of **16**: mp 176–178 °C; IR 1628, 1262, 1217, 1030, 898, 893, 888, 810, and 750 cm^{-1}; UV max 224 (log ϵ 4.59), 245 (4.57), 252 (4.64), 276 (4.80), 287 (4.95), and 301 (4.52); MS *m/e* (rel intensity) 258 (M^+, 77.5), 226 (4.2), 216 (18.6A, 215 (100), 214 (7.4), 213 (23.2). Anal. Calcd for $C_{19}H_{14}O$: C, 88.35; H, 5.46. Found: C, 88.19; H, 5.54.

10-Methoxybenz[a]anthracene (17). A solution of 2.1 g of aluminum tricyclohexaoxide in 15 mL of cyclohexanol was prepared.[12] Crystalline **7** (100 mg, 0.35 mmol) was added and the mixture refluxed for 24 h. After cooling, the reaction solution was decomposed by stirring with 100 mL of 10% HCl for 1 h. The resulting mixture was extracted with benzene (4 × 15 mL) and the organic extracts vacuum distilled to remove benzene and cyclohexanol. This yielded an oil that afforded 75 mg (84%) of **17**, mp 158–160 °C, upon crystallization from aqueous ethanol: IR 1627, 1481, 1470, 1390, 1244, 1180, 1031, 895, 887, 802, and 750 cm^{-1}; UV max 222 (log ϵ 4.58), 258 (4.61), 264 (4.70), 278 (4.81), 287 (4.82), 302 (4.27), 317 (3.94), 332 (3.93), 348 (3.79), 370 (3.55), 391 (3.55); MS *m/e* (rel intensity) 258 (M^+, 95.4), 243 (3.3), 226 (4.8), 216 (20.2), 215 (100), 214 (9.7), 213 (23.3). Anal. Calcd for $C_{19}H_{14}O$: C, 88.34; H, 5.46. Found: C, 88.10; H, 5.51.

9-Methoxybenz[a]anthracene (16). By the above procedure 45 mg of **6** yielded 26 mg (65%) of **16**, mp 175–177 °C.

10-Methoxy-7,12-dimethylbenz[a]anthracene (21). A benzene solution (2 mL) of 50 mg of **7** was added to an ethereal solution of excess MeMgI prepared by the dropwise addition of 1.5 mL of MeI to a stirred suspension of 200 mg of Mg in 7 mL of anhydrous ether. The reaction solution turned a pale yellow a few moments after addition of the dione and was allowed to stir for 45 min at room temperature. The solution was then added dropwise to a stirred solution of 1.0 mL of hydriodic acid (57%) in 2.5 mL of methanol which had been cooled in an ice bath to ~5 °C. The resultant was stirred at room temperature for 30 min. The solution was reduced to a volume of 4–5 mL by rotary evaporation at reduced pressure. Addition of 4 mL of glacial acetic acid and subsequent cooling precipitated yellow-orange crystals which were suction filtered then added to a solution of 200 mg of stannous chloride and 1 mL of concentrated HCl in 10 mL of dioxane. The resulting mixture was refluxed for 15 min and allowed to cool. Column chromatography of this material using benzene as eluting solvent yielded 27 mg (54%) of **21**, mp 136–138 °C (lit.[4] mp 137.5–138.5 °C).

8-Methoxy-7,12-dimethylbenz[a]anthracene (19). By the same procedure as above, 40 mg of **15** afforded 18 mg (45%) of **19**, mp 139–141 °C (lit.[4] mp 142–143 °C).

9-Methoxy-7,12-dimethylbenz[a]anthracene (20). Similarly, 25 mg of **6** afforded 13 mg of **20** (51%), mp 205–207 °C (lit.[5] mp 208–209.5 °C).

11-Methoxy-7,12-dimethylbenz[*a*]anthracene (22). The same method as above was applied to 100 mg of **14**, substituting 30 min of reflux for the 30 min that the MeMgI was allowed to react with the dione. Column chromatography of the final product mixture yielded a yellow oil, which crystallized from benzene–ethanol to yield 5 mg (5%) of **22**: mp 121–123 °C (lit.[4] mp 123–124 °C); MS *m/e* 286 (M^+).

Acknowledgments. We thank Dr. D. J. Wilbur for determination of the ^1H NMR spectra and for the many helpful discussions regarding their analysis. We are also grateful to Mr. S. S. Huang for his determination of the mass spectra. This research was supported by the National Cancer Institute under Contract No. N01-CO-75380 with Litton Bionetics, Inc.

Registry No.—1, 481-39-0; **2**, 29263-68-1; **3**, 100-42-5; **4**, 68796-70-3; **5**, 68796-69-0; **6**, 68757-78-8; **7**, 66240-10-6; **13**, 65915-33-5; **14**, 65915-34-6; **15**, 63019-69-2; **16**, 34570-63-3; **17**, 68757-79-9; **18**, 68757-80-2; **19**, 62064-43-1; **20**, 62078-52-8; **21**, 62064-35-1; **22**, 62064-50-0.

References and Notes

(1) Presented in part before the 175th National Meeting of the American Chemical Society, Organic Division, Anaheim, Calif., March 1978, Abstract No. 121.
(2) R. C. Moschel, W. M. Baird, and A. Dipple, *Biochem. Biophys. Res. Commun.*, **76**, 1092 (1977).
(3) A. J. Swaisland, A. Hewer, K. Pal, G. R. Keysell, J. Booth, P. L. Grover, and P. Sims, *FEBS Lett.*, **18**, 76 (1971).
(4) C. E. Morreal and V. Alks, *J. Chem. Eng. Data*, **22**, 118 (1977).
(5) J. Pataki and R. Ballick, *J. Chem. Eng. Data*, **22**, 114 (1977).
(6) M. S. Newman and S. Kumar, *J. Org. Chem.*, **43**, 370 (1978).
(7) M. S. Newman, J. M. Khanna, K. Kanakarijan, and S. Kumar, *J. Org. Chem.*, **43**, 2553 (1978).
(8) S. W. Wunderly and W. P. Weber, *J. Org. Chem.*, **43**, 2277 (1978).
(9) M. S. Newman and V. Sankaran, *Tetrahedron Lett.*, 2067 (1977).
(10) R. B. Sandin and L. F. Fieser, *J. Am. Chem. Soc.*, **62**, 2098 (1940).
(11) J. T. Traxler, *Synth. Commun.*, **7**, 161 (1977).
(12) F. U. Ahmed, T. Rangarajan, and E. J. Eisenbraun, *Org. Prep. Proced. Int.*, **7**, 267 (1975).
(13) W. B. Manning, J. E. Tomaszewski, G. M. Muschik, and R. I. Sato, *J. Org. Chem.*, **42**, 3465 (1977).
(14) G. M. Muschik, J. E. Tomaszewski, R. I. Sato, and W. B. Manning, *J. Org. Chem.*, in press.
(15) A. Wasserman, *J. Chem. Soc.*, 618 (1942).
(16) H.-J. Teuber and N. Gotz, *Chem. Ber.*, **87**, 1236 (1954).
(17) J. F. Garden and R. H. Thomson, *J. Chem. Soc.*, 2483 (1957).
(18) P. M. Brown and R. H. Thomson, *J. Chem. Soc., Perkin Trans. 1*, 997 (1976).
(19) T. J. Batterham, L. Tsai, and H. Ziffer, *Aust. J. Chem.* **18**, 1959 (1965).
(20) The Prep LC/System 500 preparative LC (Waters Associates, Inc., Milford, Mass.) performed the more difficult separation of **6** and **7** (50 mg total product) without prior cleanup of the reaction mixture. The use of toluene to elute the Porasil columns did not represent an optimization of solvent system. With this optimization and prior purification of the crude reaction mixture, separations should succeed on a larger scale.

Hydroxylation of α,β-Unsaturated Nitriles and Esters in Steroid Systems

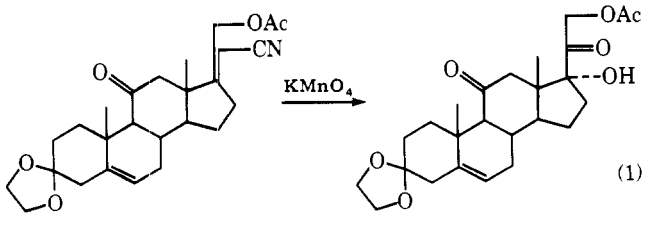
Robert W. Freerksen, Michael L. Raggio, Carrie A. Thoms, and David S. Watt*

Department of Chemistry, University of Colorado, Boulder, Colorado 80309

Received August 25, 1978

The hydroxylation of α,β-unsaturated nitriles or α,β-unsaturated esters in various steroid systems using stoichiometric amounts of osmium tetroxide furnished α-hydroxy ketones/aldehydes and α,β-dihydroxy esters in moderate yield. The absence of a C-21 acetoxy group in 17(20)-pregnene-20-carbonitriles or 5,17(20)-pregnadiene-20-carbonitriles precluded using potassium permanganate to introduce the 17α-hydroxy 20-ketone synthon. However, the stoichiometric osmium tetroxide oxidation of various 17(20)-pregnene-20-carbonitriles furnished the 17α-hydroxy 20-ketones in moderate yield. α,β-Unsaturated nitriles derived from 3-ketones and 20-ketones were also hydroxylated to give α-hydroxy ketones and aldehydes in moderate yield. No regioselectivity for the $\Delta^{17,20}$-double bond in 5,17(20)-pregnadiene-20-carbonitriles was observed using osmium tetroxide. A catalytic osmium tetroxide–potassium chlorate oxidation of 17(20)-pregnene-20-carbonitriles required zinc nitrate to sequester cyanide ion liberated in the course of the hydroxylation. A brief investigation of osmium tetroxide oxidation of 5,17(20)-pregnadienes bearing withdrawing groups at C-20 other than the nitrile disclosed an interesting hydroxylation of a 17(20)-unsaturated ester in the presence of a nonconjugated Δ^5-double bond.

Sarett[1] employed the hydroxylation of an α,β-unsaturated nitrile using osmium tetroxide in order to introduce the 17α-hydroxy-20-keto synthon found in cortico steroids. Tishler[2] and others[3,4] later modified this procedure by substituting potassium permanganate for osmium tetroxide and recorded regioselective hydroxylation of the $\Delta^{17,20}$-double bond even in the presence of a nonconjugated double bond elsewhere in the steroid as the following example[4] shows (eq 1). In connection with various synthetic interests, we needed to determine: (1) the compatibility of these procedures with other functional groups; (2) the suitability of these procedures for the synthesis of α-hydroxy aldehydes as well as α-hydroxy ketones; and (3) the feasibility of using catalytic procedures to render this reaction economical in the case of osmium tetroxide. In addition, we sought to assess the regioselectivity of attack at the 17(20)-double bond in 5,17(20)-pregnadienes which: (1) lacked a C-21 acetoxy group; and (2) possessed an electron-withdrawing group at C-20 other than a nitrile.



(1)

Results and Discussion

The α,β-unsaturated nitriles **2** and esters **3** used in this study were prepared from various steroidal ketones **1** using the phosphonate Wittig reaction.[5] We have confined our study to the α,β-unsaturated nitriles **2** derived from the condensation of ketones **1** with either diethylphosphonoacetonitrile[6] (**4**) or 2-(diethylphosphono)propionitrile[7] (**5**). As indicated in the Experimental Section, the yields of **2** were moderate to good starting with the sterically hindered C-17 and C-20 ketones. No effort was made to separate the *E*/*Z* isomers. In two cases involving the condensation of **5** with 3β-hydroxy-5α-androstan-17-one tetrahydropyranyl ether or 5-androstene-

0022-3263/79/1944-0702$01.00/0