Benzanthracene Derivatives via the Stobbe Condensation. Synthesis of 3,9-Dihydroxybenz[a]anthracene

Charles E. Morreal* and Vitauts Alks[1]

Department of Breast Surgery, Roswell Park Memorial Institute, Buffalo, New York 14263

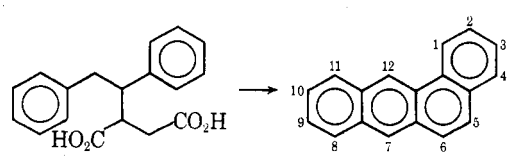
Received July 8, 1975

The synthesis of 3,9-dihydroxybenz[a]anthracene is described. The Stobbe condensation of deoxyanisoin 1 with dimethyl succinate was successful when the reaction was performed in refluxing diglyme. The resultant γ-(*p*-methoxyphenyl)-γ-(*p*-methoxybenzylidene)methylsuccinic acid (2) was reduced by Raney nickel to the saturated diacid 3, which was readily converted to its anhydride 4 in refluxing acetyl chloride. Aluminum chloride catalyzed Friedel–Crafts reaction of the anhydride in *sym*-tetrachloroethane containing 20% nitrobenzene gave 1-oxo-3-(*p*-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic acid (5), whose structure was proven by eventual conversion to 3-(*p*-methoxyphenyl)-7-methoxy-2-naphthylacetic acid (6b). The infrared spectrum of the latter unambiguously supports the structural assignment of 5. Attempted cyclization of the keto acid 5 resulted instead in the formation of an undesired enol lactone 11; therefore the ketone function was first reduced under Clemmensen conditions to the tricyclic acid 6. Anhydrous HF readily cyclized this intermediate to the hexahydrobenz[a]anthracene derivative 7. The 5-keto function was reduced either under Clemmensen or Wolff–Kishner conditions to give the deoxo derivative 8, which was aromatized with DDQ to 3,9-dimethoxybenz[a]anthracene (9a). The 3,9-diol 9b was obtained via BBr_3 cleavage of the ether, and was further characterized by conversion to the diacetate 9c. The estrogenic activities and possible carcinogenic properties of these compounds are currently under investigation.

The identification of polar metabolites of carcinogenic polycyclic hydrocarbons has been hampered by the unavailability of authentic hydroxy derivatives of these compounds. Attempts to elucidate the mechanism by which certain hydrocarbons behave as carcinogens have been limited to correlations with a meager supply of fortuitously available derivatives[2] with the exception of the easily obtainable hydroxy derivatives substituted at the 7,12 positions. No other dihydroxy derivatives of benz[a]anthracene of unequivocal structure have been reported.

Many of the polar metabolites of polycyclic hydrocarbons remain unidentified owing to the noncoincidence of these derivatives with available compounds on radiochemical scans of thin layer chromatograms. In the case of 7,12-dimethylbenz[a]anthracene, for example, a full third of the metabolites from rat liver and breast tissue incubations are more polar than the known monohydroxy derivatives of this hydrocarbon and probably contain two or more hydroxy groups.[3]

Of particular interest in this laboratory is the 3,9-diol of benz[a]anthracene, since models of this compound show that the hydroxy groups are superimposable with those of 17β-estradiol and diethyl stilbestrol, and the possibility exists that this polycyclic hydrocarbon diol may have estrogenic properties. One attractive route toward the acquisition of the benzanthracene ring system is that which has been explored by Newman.[4] This route involves the ring closure of the reduced Stobbe condensation product derived from methyl succinate and either deoxybenzoin or its methyl derivatives.



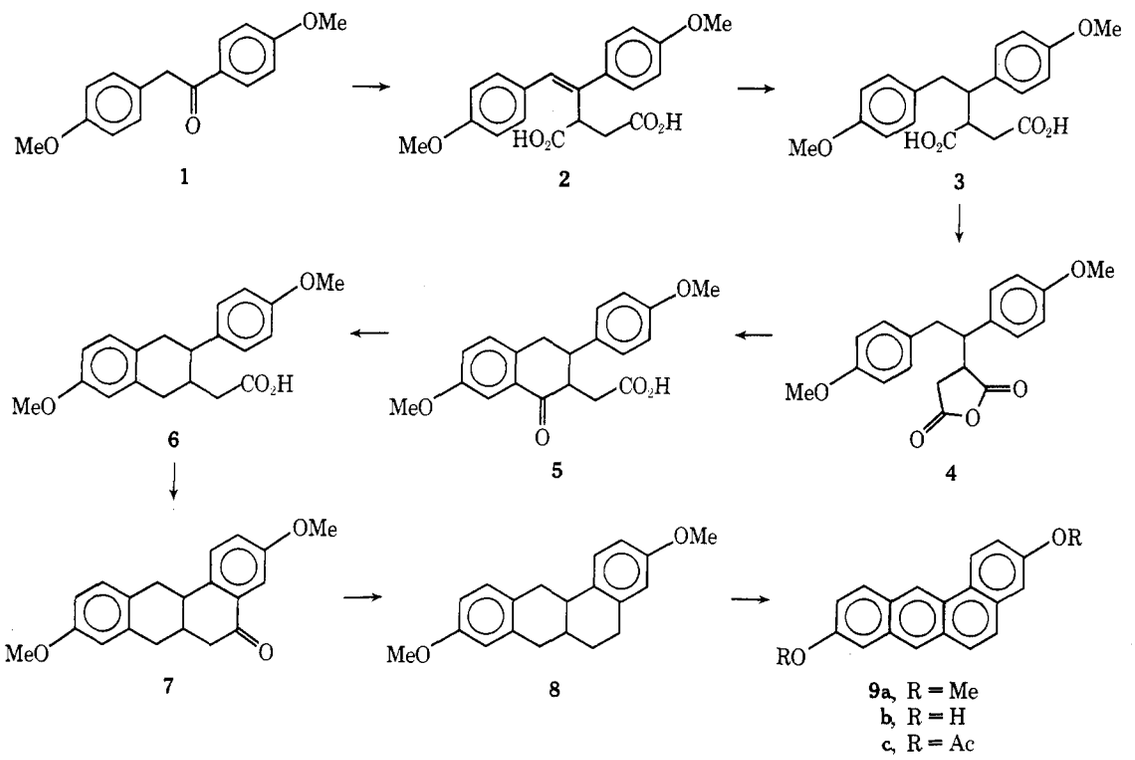
It was presumed that selection of methoxylated deoxybenzoins would yield, by similar reactions, the substituted tetracyclic benzanthracene ring system. Such an application with deoxyanisoin (1) would thus lead to the desired 3,9-dihydroxybenz[a]anthracene (9b). The expected Stobbe condensation of deoxyanisoin with dimethyl succinate, however, failed to occur under those conventional conditions[5] utilizing sodium ethoxide in ethanol or ether, sodium methoxide in ether, or potassium *tert*-butoxide in *tert*-butyl alcohol. The relative insolubility of deoxyanisoin in dimethyl succinate precluded implementation of the conditions utilized by Newman and Hart in which a solution of deoxybenzoin in dimethyl succinate was added to the hot catalyst[4].

By refluxing the reagents in diglyme and sodium methoxide, the reaction was successful, owing in part to the higher temperature of the reaction and the greater solubilizing characteristics of the solvent (see Chart I). The unsaturated acid 2 was reduced with Raney nickel in hot 10% NaOH to give saturated acid 3, mp 190–193°, and a minor isomeric saturated acid, mp 148–150°. The higher melting compound was treated with anhydrous HF in an attempt to bring about partial cyclization to compound 5 or full cyclization corresponding to the tetracyclic benz[a]anthracene ring system. The related succinic acid derivative in which the methoxyl groups are not present does indeed provide a mixture of mono- and dicyclized products under these conditions.[4] In the present case, infrared spectra of the products of the reactions gave no absorption peaks consistent with those expected from cyclic ketones. Instead, the sole product of this reaction was found to be the anhydride 4. Crude anhydride 4 was also obtained exclusively by treatment of the diacid 2 with polyphosphoric acid. Only degradation was noted by treatment of the acid 2 with either concentrated sulfuric acid or phosphorus pentachloride.

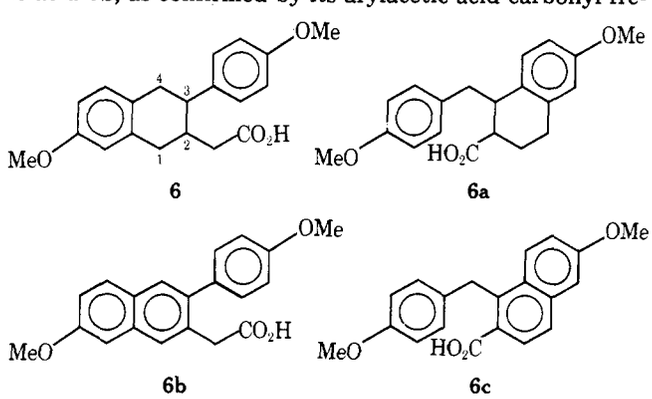
For preparative purposes, anhydride formation was most efficiently performed in refluxing acetyl chloride.[6] Cyclization of the anhydride was accomplished by aluminum chloride in *sym*-tetrachloroethane containing 20% nitrobenzene[7] to form the tricyclic keto acid 5. The assigned structure is consistent with that of the unsubstituted keto acid prepared from deoxybenzoin by Newman. To confirm the structure, it was decided to utilize the next compound in the synthetic sequence (6 in Chart I). The structural alternatives are the tetrahydronaphthylacetic acid 6 or its isomer, tetrahydronaphthoic acid 6a.

Attempts at establishing structure 6 instead of the isomer 6a by off-resonance coupling of the ^{13}C NMR spectrum of the material at hand were frustrated by the presence of a small amount of a stereoisomer at C-2 of the tetrahydronaphthalene moiety. The NMR results were equivocal in permitting assignment of a methylene vs. a

Chart I

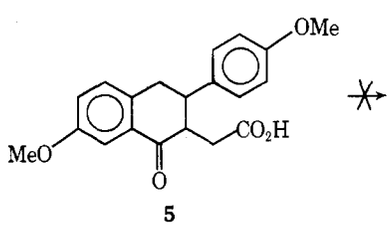


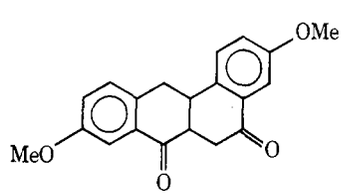
methine carbon α to the carboxyl function. Therefore, the compound was totally aromatized to give the naphthylacetic acid **6b**, as confirmed by its arylacetic acid carbonyl frequency of 1710 cm^{-1}.[8] The alternative structure **6c** is ruled out, since being a naphthoic acid, its ir carbonyl frequency would be expected to be at 1680 cm^{-1}. For purposes of comparison, spectra of 4-methoxyphenylacetic acid and 2-naphthoic acid were obtained on our instrument and showed the expected carbonyl frequencies of 1720 and 1680 cm^{-1}, respectively.

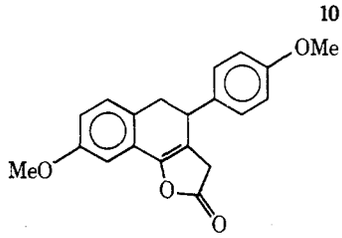


A second closure of the remaining carboxy group to form the tetracyclic benzanthracene dione **10** was attempted with thionyl chloride followed by aluminum chloride, with polyphosphoric acid, and with anhydrous HF. All of these treatments instead resulted in a compound which showed disappearance of the acid and ketone carbonyl functions (1715 and 1680 cm^{-1}, respectively) and the appearance of a single sharp peak at 1810 cm^{-1} which presumably represents the enol lactone **11**, which was not further studied.

Wolff–Kishner reduction of the keto acid **5** resulted in the formation of a single high-melting (235–239°) product which showed spectral characteristics inconsistent with the expected acid **6**. The compound was refractive to both acid and base hydrolysis and is probably a cyclic hydrazide derivative similar to those which have been demonstrated to form under these conditions with other keto acids.[9]







Clemmensen reduction successfully yielded the saturated acid **6** which easily cyclized to the tetracyclic ketone **7** with anhydrous HF. Clemmensen reduction of compound **7** gave the dimethoxyhexahydrobenz[*a*]anthracene derivative **8**. Aromatization of compound **8** to the dimethyl ether of benz[*a*]anthracene-3,9-diol **9a** was accomplished with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene[10] after it was found that only fragmentation occurred during attempted high-temperature dehydrogenation with palladium on carbon, or with selenium. The final step in the sequence was the ether cleavage with boron tribromide[11] to 3,9-dihydroxybenz[*a*]anthracene **9b**, which was further characterized by conversion to the diacetate **9c**. The estrogenic activities and the possible carcinogenic properties of the synthetic compounds described in this report are currently under investigation.

Experimental Section[12]

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzylidene)methylsuccinic Acid (2). A mixture of 100 g (0.39 mol) of deoxyanisoin 1 [p-methoxy-α-(p-methoxyphenyl)acetophenone], 57 g (0.39 mol) of dimethyl succinate, and 42.2 g (0.78 mol) of sodium methoxidein 1 l. of diglyme (2-methoxyethyl ether) was heated under reflux for 2 hr while protected from moisture with a Drierite tube. The solution was then allowed to cool to room temperature and stirred overnight. The reaction mixture was poured onto crushed ice and extracted with ether. The ether solution was extracted with a total of 1 l. of 5% NaOH. The base extracts were combined with the original aqueous phase and set up for distillation to remove residual ether. When a distillation temperature of 95° was attained, the distillation head was removed and replaced with a reflux condenser and reflux was continued for 3 hr.

The reaction solution was cooled in an ice bath, acidified with concentrated HCl, and extracted with ether. The ethereal solution was washed with water and saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 99.2 g of the crude diacid 2 as a dark glass. Crystallization from benzene afforded 48.7 g of crystals, mp 115–116°, in the first crop, and 7.64 g, mp 82–85°, in the second crop, for a total yield of 56.3 g (40.4%) of the crystalline diacid 2. Recrystallization of the higher melting crop from benzene afforded the analytical sample: mp 116–118°; ir (KBr) CO_2H, 1705; Ar, 1610; $-CH_3$, 1030 cm^{-1}. Anal. Calcd for $C_{20}H_{20}O_6$: C, 67.40; H, 5.65. Found: C, 67.66; H, 5.67.

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzyl)methylsuccinic Acid (3). To a mechanically stirred solution of 15.1 g (42.4 mmol) of diacid 2 in 500 ml of 10% NaOH on a steam bath was added 45 g of Raney nickel in small portions. When the reaction had subsided, the reaction mixture was allowed to cool to room temperature and the nickel residue was removed by filtration. The filtrate was cooled in an ice bath, stirred with a mechanical paddle-stirrer, and acidified with concentrated HCl to pH 1. The remaining white solid was separated by filtration and washed with copious amounts of cold water. The solid was dried overnight at room temperature and then at 100° over P_2O_5, and gave 14.1 g (93%) of saturated diacid 3, mp 180–183°. Crystallization from ethanol afforded the analytical sample: mp 198–200°; ir (KBr) CO_2H, 1695; Ar, 1610; $-OCH_3$, 1035 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found: C, 67.23; H, 6.15.

The mother liquors also yielded a small amount of a lower melting isomer in some runs. This isomer, mp 148–150°, had ir spectrum which was virtually superimposable with that of the higher melting isomer, with minor differences in the fingerprint region. Anal. Calcd for $C_{20}H_{22}O_6$: C, 67.04; H, 6.19. Found: C, 67.12; H, 6.20.

γ-(p-Methoxyphenyl)-γ-(p-methoxybenzyl)methylsuccinic Anhydride (4). A mixture of 20.0 g (55.8 mmol) of higher melting diacid 3 and 40 ml of acetyl chloride was refluxed for 1 hr. The excess acid chloride was removed in vacuo and the last traces of acetic acid were removed azeotropically with benzene. The remaining yellow glass of crude anhydride was used directly in the Friedel–Crafts reaction: ir ($CHCl_3$) anhydride C=O, 1870, 1780; Ar, 1620; $-OCH_3$, 1030 cm^{-1}.

1-Oxo-3-(p-methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic acid (5). To a stirred, ice-cold solution of 11.1 g (83 mmol) of $AlCl_3$ in 120 ml of *sym*-tetrachloroethane and 30 ml of nitrobenzene was added a solution of 14.1 g (40.3 mmol) of anhydride 4 in the same solvent mixture as above. The addition was performed in a dropwise fashion over a period of 50 min. The mixture was stirred at 0–5° for 2 hr and then allowed to warm to room temperature overnight. The dark brown reaction mixture was poured onto a mixture of 10% HCl and crushed ice, and extracted with chloroform. The organic phase was extracted with 5% NaOH; the latter was cooled to 0° and acidified with concentrated HCl. The precipitated oil was extracted into chloroform, washed with water, dried ($MgSO_4$), and concentrated in vacuo gave 12.7 g (89.5%) of crude tricyclic keto acid 5. Crystallization from benzene–hexane afforded the analytical sample: mp 151–152°; ir (KBr) CO_2H, 1705; C=O, 1675; Ar, 1610; $-OCH_3$, 1038 cm^{-1}; NMR ($CDCl_3$)δ 2.4–3.3 m, 6 H), 3.82 (s, 3 H), 3.85 (s, 3 H), 6.8–7.6 (m, 7 H). Anal. Calcd for $C_{20}H_{20}O_5$: C, 70.57; H, 5.92. Found: C, 70.66; H, 5.93.

3-(p-Methoxyphenyl)-7-methoxy-1,2,3,4-tetrahydro-2-naphthylacetic Acid (6). Amalgamated zinc was prepared by swirling 30 g of mossy zinc granules with 3.0 g of $HgCl_2$, 1.5 ml of concentrated HCl, and 38 ml of H_2O for 5 min. The solvent was decanted, and to the residual amalgamated zinc was added 18 ml of H_2O, 40 ml of concentrated HCl, and a solution of 9.02 g (25.5 mmol) of keto acid 5 in 100 ml of toluene. The reaction mixture was stirred under reflux for 69 hr. During the course of the reaction, seven 10-ml portions of concentrated HCl were added at intervals. The reaction mixture was cooled in an ice bath, and the biphasic solution was decanted from the residual metal and extracted with benzene. The organic solution was extracted with two 100-ml portions of 5% NaOH; to the base solution was added 10 ml $(CH_3)_2SO_4$ and the mixture was stirred at room temperature for 1 hr. The reaction mixture was cooled in an ice bath, acidified with concentrated HCl, extracted with chloroform, washed with water, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo to give 7.61 g (88%) of crude acid 6 as a light yellow glass. Crystallization from benzene gave a solid, mp 147–156°, which on recrystallization afforded the analytical sample: mp 153–156°; ir (KBr) CO_2H, 1700; Ar, 1610; $-OCH_3$, 1035 cm^{-1}; NMR ($CDCl_3$) δ 2.1–3.0 (m, 8 H), 3.74 (s, 6 H), 6.56–7.33 (m, 7 H). Anal. Calcd for $C_{20}H_{22}O_4$: C, 73.6; H, 6.79. Found: C, 73.53; H. 6.80.

3-(p-Methoxyphenyl)-7-methoxy-2-naphthylacetic Acid (6b). A solution of 1.0 g (3.06 mmol) of acid 6 and 2.09 g (9.18 mmol) of DDQ in 50 ml of anhydrous benzene was refluxed for 18.5 hr while protected from moisture with a Drierite tube. The reaction mixture was cooled to room temperature, and the suspended precipitate was removed by filtration and washed with benzene. The filtrate was passed through a column (45 × 90 mm) of activated alumina (80–225 mesh, MCB) and eluted with ethyl acetate (2 × 500 ml) and 5% CH_3CO_2H in ethyl acetate (2 × 500 ml). Concentration of the combined eluates gave 0.80 g of tan foam whose ir spectrum showed, in addition to the expected 1710-cm^{-1} acid peak, an ester peak at 1765 cm^{-1}, presumably due to transesterification by ethyl acetate on the activated alumina column. The material was therefore refluxed in 10% NaOH (50 ml) for 4 hr, cooled in an ice bath, and acidified with concentrated HCl to give a tan solid. This was separated by filtration, washed with water, and dried in vacuo at room temperature over P_2O_5 to give 0.75 g of crude naphthylacetic acid **6b.** Recrystallization from methanol afforded the analytical sample: mp 218–220°; ir ($CHCl_3$) $-CO_2H$, 1710; Ar, 1630, 1620; $-OCH_3$, 1030 cm^{-1}; NMR ($CDCl_3$) δ 3.77 (s, 2 H), 3.86 (s, 3 H), 3.94 (s, 3 H), 6.78–7.85 (m, 9 H). Anal. Calcd for $C_{20}H_{18}O_4$: C, 74.52; H, 5.63. Found: C, 74.25; H, 5.61.

3,9-Dimethoxy-5-keto-5,6,6a,7,12,12a-Hexahydrobenz[a]anthracene (7). A 4.64-g (14.2 mmol) sample of the naphthylacetic acid 6 was dissolved in 60 ml of anhydrous HF and allowed to evaporate overnight. The crystalline residue was partitioned between chloroform and water, washed with 5% NaOH solution, washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 4.44 g of a greenish glass. The infrared spectrum of this material showed, in addition to the desired 1680-cm^{-1} carbonyl absorption of the tetracyclic ketone 7, a minor ester peak at 1725 cm^{-1}. To remove the latter contaminant, the above material was refluxed with 25 ml of 10% NaOH and 30 ml of ethanol for 1 hr. The reaction mixture was cooled in an ice bath and the suspended solid was separated by filtration, washed with water, and dried in vacuo at 100° over P_2O_5 to give 2.69 g of tetracyclic ketone 7. The mother liquors yielded another 0.57 g of material for a total of 3.26 g (74.3%). Recrystallization from methanol provided the analytical sample: mp 145–147°; ir ($CHCl_3$) C=O, 1680; Ar, 1620; $-OCH_3$, 1027 cm^{-1}; NMR ($CDCl_3$) δ 2.12–3.68 (m, 8 H), 3.79 (s, 3 H), 3.86 (s, 3 H), 6.60–7.63 (m, 6 H). Anal. Calcd for $C_{20}H_{20}O_3$: C, 77.9; H, 6.54. Found: C, 77.94; H, 6.56.

3,9-Dimethoxy-5,6,6a,7,12,12a-Hexahydrobenz[a]anthracene (8). A. Via Clemmensen Reduction. Amalgamated zinc was prepared from 7 g of mossy zinc, 0.7 g of $HgCl_2$, 1.2 ml of concentrated HCl, and 10 ml of H_2O in the usual fashion. To the amalgamated metal was added 5 ml of H_2O, 13 ml of concentrated HCl, and a solution of 1.90 g (6.17 mmol) of the tetracyclic ketone 7 in 100 ml of toluene. The mixture was refluxed with stirring for 21 hr, during which period five 5-ml portions of concentrated HCl were added at intervals. The reaction mixture was cooled to room temperature, partitioned between benzene and water, washed with saturated NaCl solution, dried ($MgSO_4$), and concentrated in vacuo gave 1.85 g of crude solid tetracyclic compound 8. Recrystallization from benzene–hexane afforded the analytical sample: 1.19 g (66%); mp 130–131°; ir($CHCl_3$) no C=O; Ar, 1610, 1580; $-OCH_3$, 1030 cm^{-1}. Anal. Calcd for $C_{20}H_{22}O_2$: C, 81.60; H, 7.53. Found: C, 81.55; H, 7.55.

B. Via Wolff–Kishner Reduction. A mixture of 3.26 g (10.6 mmol) of tetracyclic ketone 7, 2.78 g (86.7 mmol) of anhydrous hydrazine, and 3.01 g (53 mmol) of KOH in 100 ml of diethylene glycol was refluxed with stirring for 4 hr and left to stir overnight at

room temperature. The reaction mixture, which contained a suspended solid, was diluted with water and acidified with concentrated HCl. The solid was separated by filtration and washed with water. Recrystallization from benzene gave 1.35 g (43.3%) of material, mp 109–112°, which on further recrystallization gave material identical with that obtained from Clemmensen reduction: NMR ($CDCl_3$) δ 1.42–3.55 (m, 10 H), 3.88 (s, 6 H), 6.58–7.40 (m, 6 H).

3,9-Dimethoxybenz[*a*]anthracene (9a). A solution of 200 mg (0.678 mmol) of the hexahydro compound **8** and 930 mg (4.07 mmol) of DDQ (2,3-dichloro-5,6-dicyano-1,4-benzoquinone) in 60 ml of benzene was refluxed for 16 hr. The reaction mixture was cooled to room temperature, filtered through an alumina column, and eluted with benzene. The colorless eluate on concentration gave 190 mg of white crystals, fluorescent in ultraviolet light, mp 175–176°. Recrystallization from benzene–hexane afforded the analytical sample of **9a** as colorless needles: mp 190–192°; ir (KBr) Ar, 1625, 1590; $-OCH_3$, 1025 cm^{-1}; NMR ($CDCl_3$) δ 3.98 (s,6 H), 7.24–8.94 (m, 10 H). Anal. Calcd for $C_{20}H_{16}O_2$: C, 83.31; H, 5.59. Found: C, 83.05; H, 5.67.

3,9-Dihydroxybenz[*a*]anthracene (9b). To a heated, stirred solution of 394 mg (1.36 mmol) of 3,9-dimethoxybenz[*a*]anthracene (**9a**) in 30 ml of benzene was added a solution of 3 ml of BBr_3 in 10 ml of benzene. Initially, during the dropwise addition of the latter, a precipitate was formed which redissolved on further heating. The solution was refluxed for 3 hr protected from moisture with a Drierite tube, then cooled to room temperature, poured onto crushed ice, and extracted with ether. The organic solution was washed with water and extracted with 10% NaOH (3 × 35 ml). The fluorescent yellow base solution was cooled to 0°, acidified with concentrated HCl, and extracted with ethyl acetate. The organic extract was washed with water, dried ($MgSO_4$), and concentrated in vacuo to give 370 mg of brown solid, mp >250° dec. High vacuum sublimation of this material at 255° afforded analytically pure diol **9b** as a yellow solid: mp 265–270° dec; ir (KBr) –OH, 3100; Ar, 1620, 1595 cm^{-1}. Anal. Calcd for $C_{18}H_{12}O_{12}$: C, 83.06; H, 4.65. Found: C, 82.89; H, 4.68.

3,9-Diacetoxybenz[*a*]anthracene (9c). A 125-mg sample of the dihydroxy compound **9b** was dissolved in 5 ml each of acetic anhydride and pyridine, and left overnight at room temperature. The usual work-up afforded analytically pure diacetate **9c** as white platelets: mp 200–201°; ir (KBr) C=O, 1760; Ar, 1620, 1590 cm^{-1}; NMR ($CDCl_3$) δ 2.38 (s, 6 H), 7.18–9.10 (m, 10 H). Anal. Calcd for $C_{22}H_{16}O_4$: C, 76.73; H, 4.68. Found: C, 76.56; H, 4.70.

Acknowledgment. We would like to thank Mr. Norman Angelino, of Dr. Walter Korytnyk's laboratory in this institute, for help in NMR spectral determinations on the Varian XL100 spectrometer, and Dr. Alan J. Solo, Department of Medicinal Chemistry, State University of New York at Buffalo, for helpful discussion on spectral data.

Registry No.—**1**, 120-44-5; **2**, 56554-10-0; **3**, 56554-11-1; **4**, 56554-12-2; **5**, 56554-13-3; **6**, 56554-14-4; **6b**, 56554-15-5; **7**, 56554-16-6; **8**, 56554-17-7; **9a**, 56554-18-8; **9b**, 56614-97-2; **9c**, 56554-19-9; dimethyl succinate, 196-65-0.

References and Notes

(1) This work was supported predominantly by Grant CA-015162 and in part by Grant PO1-CA-16056 of the National Institutes of Health.
(2) L. F. Fieser and E. B. Hershberg, *J. Am. Chem. Soc.*, **60**, 1893 (1938).
(3) T. S. Tamulski, C. E. Morreal, and T. L. Dao, *Cancer Res.*, **33**, 3117 (1973).
(4) M. S. Newman and R. T. Hart, *J. Am. Chem. Soc.*, **69**, 298 (1947).
(5) W. S. Johnson and G. H. Daub, *Org. React.* **6**, 1 (1951).
(6) L. F. Fieser and E. L. Martin, "Organic Syntheses", Collect. Vol. II, Wiley, New York, N.Y., 1943, p 560.
(7) R. D. Haworth and G. Sheldrick, *J. Chem. Soc.*, 636 (1935).
(8) K. Nakanishi, "Infrared Absorption Spectroscopy", Holden-Day, San Francisco, Calif., 1962, p 43.
(9) D. Todd, *Org. React.*, **6**, 378 (1948).
(10) E. A. Braude, A. G. Brook, and R. P. Linstead, *J. Chem. Soc.*, 3569 (1954).
(11) D. L. Manson and O. C. Musgrave, *J. Chem. Soc.*, 1011 (1963).
(12) Analyses were performed by Galbraith Laboratories, Knoxville, Tenn., and mostly by Atlantic Microlab, Atlanta, Ga. Melting points were determined in open capillaries on a Mel-Temp apparatus and are uncorrected. The NMR spectra were determined with a Varian A-60 or Varian XL-100 spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. The ir spectra were determined in KBr pellets or $CHCl_3$ solution on a Perkin-Elmer 137 spectrometer.

Synthesis of 1-Substituted and 1,3-Disubstituted 5-Hydantoincarboxylates[1]

J. P. Li

Research Laboratories of the Aldrich Chemical Company, Inc., Milwaukee, Wisconsin 53233

Received May 12, 1975

N-Substituted aminomalonates react with KCNO or isocyanates to give directly 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates. The initial products, i.e., the hitherto unknown N-substituted or N,N′-disubstituted ureidomalonates, cyclize spontaneously on heating under the experimental conditions. This behavior is in contrast to that of ureidomalonate and N′-substituted ureidomalonates, which require base catalysis for cyclization. The benzylic protons of 1-benzyl-5-hydantoincarboxylates display chemical shift nonequivalence.

In a synthetic program for 8-hydroxypurines, it was necessary to prepare ethyl 1-substituted 5-hydantoincarboxylates. A literature search has not revealed a description of any 1-substituted or 1,3-disubstituted 5-hydantoincarboxylates,[2] although 3-substituted 5-hydantoincarboxylates[3,4] are known. We wish to report a facile general synthesis of the title 5-hydantoincarboxylates by the cyclization of N-substituted and N,N′-disubstituted ureidomalonates.

5-Hydantoincarboxylate (**1k**) and many 3-substituted 5-hydantoincarboxylates are known and can be prepared by base-catalyzed cyclization of ureidomalonate (**4a**) and N′-substituted ureidomalonates.[3-5] However, under no circumstances can the cyclization be effected simply by heating. Gatewood[2h] reported that **4b** failed to cyclize to **1j** under various conditions, including heating at its melting point for varying lengths of time. We noted that **4a** behaved similarly. Heating **4a** beyond its melting point, e.g., at 200°, caused gas evolution and numerous products were formed, as indicated by the TLC of the residue. An apparent route to 1-substituted 5-hydantoincarboxylates would be, therefore, the base-catalyzed cyclization of N-substituted ureidomalonates.

1-Substituted 5-Hydantoincarboxylates. Heating *N*-methyl- (**2a**) and *N*-benzylaminomalonate hydrochloride (**2b**) with KCNO in water produced directly 1-methyl- (**1a**) and 1-benzyl-5-hydantoincarboxylate (**1e**), respectively (method A). The initial products, i.e., the N-substituted ureidomalonates **4c** and **4d**, apparently cyclized spontaneously under the experimental conditions. This result is surprising in view of the fact that the reaction of amino-