Nazionale delle Ricerche (Rome).

Registry No. 1, 5703-26-4; 2, 60-12-8; 3, 103-82-2; 4, 699-02-5; 5, 622-47-9; 6, 702-23-8; 7, 104-01-8; 8, 100-51-6; 9, 122-97-4; 10, 111-27-3; 11, 108-93-0; 12, 108-94-1; p-$OCH_3C_6H_4CHO$, 123-11-5; C_6H_5CHO, 100-52-7; p-$CH_3C_6H_4CHO$, 104-87-0; C_6H_5COOH, 65-85-0; p-$CH_3C_6H_4COOH$, 99-94-5; $PhCH_2CH_2COOH$, 501-52-0; p-$OCH_3C_6H_4COOH$, 100-09-4; γ-MnO_2, 1313-13-9; hexanoic acid, 142-62-1; adipic acid, 124-04-9.

Synthesis of Methylene-Bridged Polycyclic Hydrocarbons

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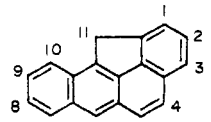
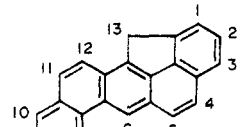
In connection with studies on the mechanism(s) of hydrocarbon carcinogenesis,[1] we required several methylene-bridged derivatives of carcinogenic polycyclic hydrocarbons, such as 1,12-methylenebenz[a]anthracene (**1**) and 1,14-methylenedibenz[a,h]anthracene (**2**). It was anticipated that the methylene function might interfere with enzymatic activation to the ultimate carcinogenic bay region diol epoxide metabolites.[1]



1



2

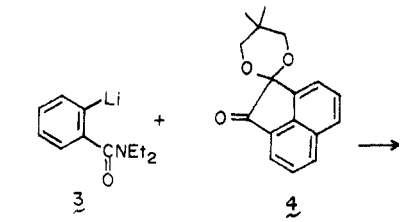
However, few such hydrocarbons are known.[2] The sole prior synthesis of **1** was a 10-step sequence from acenaphthylene described by Fieser and Cason in 1940.[3] We now report more convenient syntheses of **1** and **2** from the readily available 1,2-acenaphthylenedione in only five steps each.

Results and Discussion

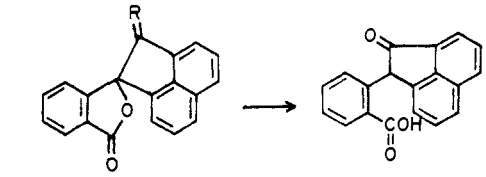
In initial exploratory studies, we attempted to utilize a method involving in the initial step condensation of an α-lithioaryl amide with an aryl ketone or aldehyde.[4] However, reaction of 2-lithio-*N,N*-diethylbenzamide (**3**) with 1(2*H*)-acenaphthylenone or its 2,2-dideuterio derivative failed to provide the desired lactone (**5a**). Apparently enolization is favored over addition to the carbonyl function.

The 2,2-dimethyl-1,3-propylene monoketal of 1,2-acenaphthylenedione (**4**) was conveniently prepared by acid-catalyzed reaction of 2,2-dimethylpropane-1,3-diol with 1,2-acenaphthylenedione by the method of Merric and Ghera.[5] Reaction of **3** with **4** took place smoothly at −70 °C to furnish the desired lactone **5b** in excellent yield (93%).

Treatment of **5b** with BF_3·Et_2O provided the keto lactone **5c**, which underwent reduction with zinc and alkali to the keto acid **6**. The latter was also obtained directly from **5b** by treatment with zinc and alkali. Cyclization of **6** with $ZnCl_2$ and acetic anhydride in acetic acid in the usual manner[4] yielded the acetoxy ketone **7a**, which on treatment with CH_3ONa in methanol gave the free phenolic ketone **7b**. The latter was more efficiently synthesized directly from **6** by cyclization in liquid HF. Attempted reduction of **7b** with $LiAlH_4$ and $AlCl_3$ failed to provide a pure product. Reduction of **7b** with hydriodic acid and red phosphorus in acetic acid[6] did not yield 1,12-methylenebenz[a]anthracene (**1**) as expected but furnished instead the product of its further hydrogenation, 4,5-dihydro-1,12-methylenebenz[a]anthracene (**8**). Dehydrogenation of the latter with o-chloranil or DDQ gave **1**.

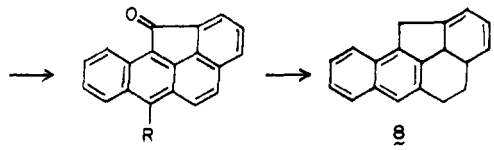


3 **4**



5a: R = H_2
b: R = $(CH_3)_2C(CH_2O)_2$
c: R = O

6



7a: R = OAc
b: R = OH

8

The site of hydrogen addition in **1** is unusual, since reduction of the benz[a]anthracene ring system by HI normally takes place in the meso ring[6] (i.e., the 6,10a-positions). The structure of **8** was clearly differentiated from 6,10a-dihydro-**1** by its proton NMR spectrum, which showed a pair of triplets (δ 3.19 and 3.29) assigned to the H_4 and H_5 methylene protons and a methylene singlet at δ 4.14. Preferential hydrogen addition in the 4,5-positions of **1** may be a consequence of steric strain that is relieved in the product.

Synthesis of 1,14-methylenedibenz[a,h]anthracene (**2**) was accomplished from the same starting material via an analogous sequence. Reaction of 2-lithio-*N,N*-diethylnaphthamide (**9**) with **4** furnished the lactone intermediate **10**. Treatment of the latter with zinc and alkali gave the keto acid **11**, which underwent cyclization in liquid HF to the phenolic ketone **12**. Reduction of **12** with hydriodic acid and red phosphorus in acetic acid furnished **2** directly.

The synthetic method outlined provides a potentially general procedure for the synthesis of methylene-bridged polycyclic hydrocarbons.

Experimental Section

General Methods. 2-Lithio-*N,N*-diethylbenzamide (**3**) and 2-lithio-*N,N*-diethyl-1-naphthamide (**9**) were generated in situ by directed ortho metalation of *N,N*-diethylbenzamide and *N,N*-diethyl-1-naphthamide, respectively, by the methods previously

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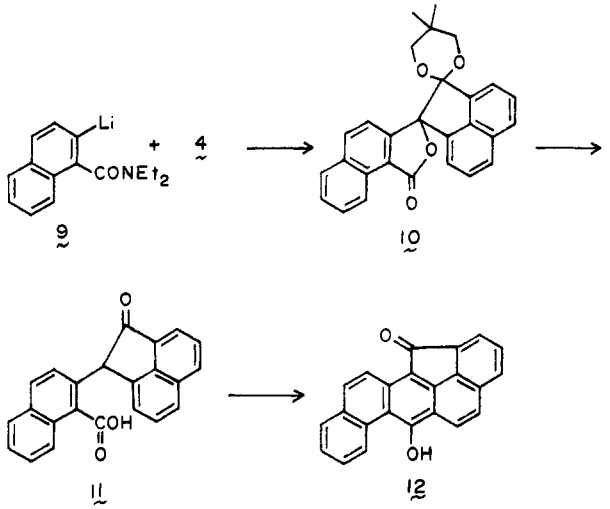

described.[4,7,8] *N,N,N',N'*-Tetramethylenediamine (TMEDA) was distilled from KOH, and tetrahydrofuran (THF) was distilled from $LiAlH_4$ immediately prior to use. *sec*-Butyllithium in cyclohexane (1.25 M), 1-acenaphthylenol, 1,2-acenaphthylenedione, and 2,2-dimethylpropane-1,3-diol were purchased from the Aldrich Chemical Co. 1(2*H*)-Acenaphthylenone was synthesized from 1-acenaphthylenol through chromic acid oxidation by the method of Fieser.[3] The NMR spectra were recorded on a Varian EM 360 and/or the University of Chicago 500-MHz spectrometer in $CDCl_3$ with tetramethylsilane as an internal standard. Melting points are uncorrected. All new compounds gave satisfactory analyses for C and H within ±0.3%.

Preparation of the 2,2-Dimethylpropylene Monoketal of 1,2-Acenaphthylenedione (4). A solution of 1,2-acenaphthylenedione (500 mg, 3 mmol), 2,2-dimethylpropane-1,3-diol (300 mg, 3.3 mmol), and *p*-toluenesulfonic acid (30 mg) in dry benzene (10 mL) was refluxed for 20 h in a flask equipped with a Dean–Stark trap. The reaction mixture was diluted with ether, washed with aqueous $NaHCO_3$ and NaCl solutions, and dried ($MgSO_4$). Removal of the solvent and chromatography on a column of silica gel eluted with hexane–benzene furnished 4 (500 mg, 70%): mp 109 °C (ether–petroleum ether); NMR δ 0.9 (s, 3, CH_3), 1.6 (s, 3, CH_3), 3.4–4.8 (m, 4, CH_2), 7.5–8.1 (m, 6, aromatic).

Reaction of 2-Lithio-*N,N*-diethylbenzamide (3) with 4. To a solution of **3**, prepared as previously described[4,8] from *N,N*-diethylbenzamide (1.4 g, 8 mmol) at −70 °C under an argon atmosphere, was added 2.1 g (8 mmol) of **4**. The deep violet color rapidly changed to yellow. The mixture was stirred overnight at ambient temperature and then acidified with cold dilute HCl and worked up conventionally to afford 3.2 g of a yellow solid. This product was dissolved in benzene (320 mL), and *p*-toluenesulfonic acid (320 mg) was added. The solution was heated at reflux for 4 h, using a Dean–Stark trap to separate water. After cooling, the benzene solution was washed with $NaHCO_3$ solution, water, dried ($MgSO_4$), and evaporated to dryness. Crystallization of the product from THF furnished 2.7 g (93%) of **5b**: mp 250–251 °C; NMR δ 0.7 (s, 3, CH_3), 1.2 (s, 3, CH_3), 2.9–3.9 (m, 4, CH_2), 7.0–8.1 (m, 10, aromatic); MS (70 eV), *m/e* 372 (M^+).

Reduction of Ketal Lactone 5b to Keto Acid 6. 1. Direct Reduction. A mixture of **5b** (500 mg), zinc (5 g activated with $CuSO_4$), 10% KOH (50 mL), and pyridine (5 mL) was refluxed with stirring for 20 h. The reaction mixture was cooled and filtered through Celite. Acidification of the filtrate with dilute HCl furnished the keto acid **6**, which was extracted with EtOAc, washed with water, and dried ($MgSO_4$). Removal of the solvent and crystallization from EtOAc gave 350 mg (92%) of **6**: mp 180 °C dec; NMR δ 7.25–8.70 (m, 11, benzylic and aromatic); MS (70 eV), *m/e* 288 (M^+).

2. Preparation of 6 via 5c. A solution of **5b** (52 mg) and BF_3·Et_2O (0.3 mL) in CH_2Cl_2 (18 mL) was stirred at room temperature for 1.5 h. The usual workup furnished 36.4 mg of **5c** (90%): mp 176–177 °C (CH_2Cl_2–ether); NMR δ 6.8–8.3 (m, 10, aromatic). Reduction of **5c** (150 mg) with zinc and alkali by the procedure employed for **5b** gave 120 mg (80%) of **6**: mp and mmp 179 °C dec.

6-Hydroxy-11-oxo-1,12-methylenebenz[*a*]anthracene (7b). A solution of the keto acid **6** (60 mg) in liquid HF (~20 mL) was stirred overnight and then evaporated to dryness and partitioned between aqueous Na_2CO_3 and ether. The organic layer was washed with water and dried ($MgSO_4$). Removal of the solvent furnished 50 mg (89%) of **7b**: mp 225–226 °C (EtOAc); NMR (500 MHz) δ 7.50 (t, 1, H_2), 7.58–7.63 (dd, 2, H_4 and H_5), 7.81 (d, 1, H_3, J = 8 Hz), 7.84 (s, 1, OH), 7.89–7.94 (m, 2, H_8 and H_9), 8.07 (d, 1, H_7, $J_{7,8}$ = 7 Hz), 8.10 (d, 1, H_1, $J_{1,2}$ = 8 Hz), and 8.40 (d, 1, H_{10}, $J_{9,10}$ = 7 Hz).

Compound **7b** was also prepared from **6** via **7a** by $ZnCl_2$-catalyzed cyclization in the presence of Ac_2O.[4] A mixture of **6** (400 mg), $ZnCl_2$ (150 mg), AcOH (32 mL), and Ac_2O (16 mL) was refluxed with stirring for 2 h. The solution was cooled and then poured into ice–water, and the precipitate was filtered, washed with water, and dried in vacuo. Crystallization from EtOAc gave 350 mg of **7a** (81%): mp 153 °C; NMR δ 7.25–8.45 (m, 9, aromatic), 2.15 (s, 3, CH_3). Treatment of **7a** with excess $NaOCH_3$ in THF for 50 min gave **7b**: mp and mmp 225 °C.

4,5-Dihydro-1,12-methylenebenz[*a*]anthracene (8). A mixture of **7b** (600 mg), HI (6 mL of 57% solution), glacial acetic acid (60 mL), and red phosphorus (600 mg) was heated under reflux for 20 h. The usual workup followed by chromatography on a column of silica gel eluted with benzene–hexane furnished **8** (300 mg, 56%) as a white crystalline solid: mp 125 °C (ether–benzene); NMR (500 MHz) δ 3.19 (t, 2, CH_2), 3.30 (t, 2, CH_2), 4.14 (s, 2, CH_2), 7.15 (d, 1, H_3, J = 7 Hz), 7.22 (t, 1, H_2), 7.39 and 7.44 (2 t, 2, H_8 and H_9), 7.42 (d, 1, H_7, J = 7 Hz), 7.84 (d, 1, H_1 or H_{10}, J = 8 Hz), 7.9 (d, 1, H_1 or H_{10}, J = 8 Hz); MS (70 eV), *m/e* 242 (M^+).

1,12-Methylenebenz[*a*]anthracene (1). A mixture of **8** (60 mg) and excess DDQ or *o*-chloranil in benzene (60 mL) was refluxed with stirring under N_2 for 4 h. Filtration through a column of neutral alumina eluted with hexane–benzene gave a solid product that was crystallized from benzene–hexane to yield 25 mg (42%) of **1**: mp 123 °C (lit.[3] mp 122.5–123 °C); NMR δ 4.2 (s, 2, CH_2), 7.1–8.3 (m, 9, aromatic), 8.5 (s, 1, H_6).

Reaction of 2-Lithio-*N,N*-diethylnaphthamide (9) with 4. To a solution of **9**, prepared as previously described[4,8] from *N,N*-diethylnaphthamide (5.9 g, 26 mmol) at −60 to −80 °C under N_2, was added a solution of **4** (7 g, 26 mmol) in THF (10 mL). Ether (50 mL) was added and stirring was continued at the same temperature for 1 h. Then the temperature was allowed to rise to ambient temperature slowly over a 10-h period. The reaction was worked up in the usual manner to yield 14 g of crude product. This was dissolved in $CHCl_3$ (100 mL) and cyclohexane (10 mL) and refluxed for 2 h to ensure complete conversion to the lactone. Removal of the solvent and trituration with ether furnished 9.6 g (87%) of the ketal lactone **10**: mp 246 °C (THF); NMR δ 0.65 (s, 3, CH_3), 1.20 (s, 3, CH_3), 3.50–3.90 (m, 4, CH_2), 7.00–8.10 (m, 12, aromatic), 9.2 (d, 1, aromatic, J = 6 Hz).

Reduction of Ketal Lactone 10 to the Keto Acid 11. Reduction of **10** (6.2 g, 14.6 mmol) with zinc and alkali by the procedure described for preparation of **7** (reaction time 12 h) gave 4.6 g (94%) of **11**: mp 204 °C dec (EtOAc); NMR δ 7.4 (s, 1, methine), 7.7–8.9 (m, 12, aromatic).

6-Hydroxy-13-oxo-1,14-methylenedibenz[*a*,*h*]anthracene (12). Overnight reaction of **11** (2.3 g, 6.8 mmol) in liquid HF (~100 mL) and the usual workup procedure followed by passage through a short column of Florisil furnished 1.79 g (82%) of **12**: mp 260 °C (CH_2Cl_2); NMR δ 7.1–8.25 (m, 10 aromatic), 9.1 (d, 1, H_7).

Cyclization of **11** (3 g, 8.8 mmol) with $ZnCl_2$ (500 mg), Ac_2O (35 mL), and AcOH (75 mL) by the method employed for **7b** followed by chromatography of the product on Florisil gave 2.2 g (78%) of **12**: mp 260 °C, mixture melting point with authentic **14** did not depress.

1,14-Methylenedibenz[*a*,*h*]anthracene (2). Reduction of **12** (210 mg, 0.6 mmol) with HI afforded pale yellow crystals of **2**: 55%; mp 260–262 °C (benzene–hexane) [lit.[3] mp 266–267 °C (corr)]; NMR (500 MHz) δ 4.60 (s, 2, CH_2), 7.60 (t, 1, H_2), 7.62 (t, 1, H_9), 7.65 (t, 1, H_8), 7.70–7.82 (m, 4, H_1 or H_3, H_4, H_{10}, H_{11}),

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7.87 (d, 1, H_1 or H_3), 7.94 (d, 1, H_5), 8.02 (d, 1, H_{12}), 9.13 (d, 1, H_7), 9.30 (s, 1, H_6) ($J_{2,3}$ = 7.8, $J_{4,5}$ = 8.6, $J_{7,8}$ = 8.8, $J_{11,12}$ = 8.7 Hz).

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Registry No. 1, 202-94-8; 2, 201-42-3; 3, 81380-82-7; 4, 84877-34-9; 5b, 84877-35-0; 5c, 84877-36-1; 6, 84877-37-2; 7a, 84895-09-0; 7b, 84877-38-3; 8, 84877-39-4; 9, 78618-70-9; 10, 84877-40-7; 11, 84877-41-8; 12, 84877-42-9; 1,2-acenaphthylenedione, 82-86-0; *N,N*-diethylbenzamide, 1696-17-9; *N,N*-diethyl-1-naphthamide, 5454-10-4.

σ Adducts of 5-Nitropyrimidines with Liquid Ammonia and Their Oxidation into Aminonitropyrimidines[1]

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Received August 2, 1982

The reactivity of azines toward potassium amide or liquid ammonia to form anionic σ complexes or neutral σ adducts has been the subject of numerous publications.[2] Highly electrophilic azines such as pteridines,[3] tetrazines,[4] or quaternary pyrimidinium salts[5] were found to react with liquid ammonia (free of amide ions) to give the corresponding amino adducts. These dihydro compounds can be regarded as intermediates in the nucleophilic displacement of hydrogen by ammonia.[6] Indeed, it has recently been shown that when 3-(*R*)-1,2,4,5-tetrazines[7] or pteridines[8] interact with liquid ammonia in the presence of potassium permanganate, the intermediate amino σ adducts were immediately oxidized to the corresponding amination products (Scheme I).

Because of the rather mild conditions that can be applied (low temperatures, no need to use the strong nucleophilic potassium amide) and good yields, this modification of the Chichibabin amination seems to be a very attractive and promising procedure for direct amination of azines.

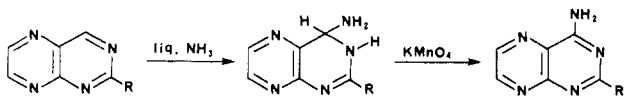
This paper describes the further successful application of this method in pyrimidine chemistry.

Results and Discussion

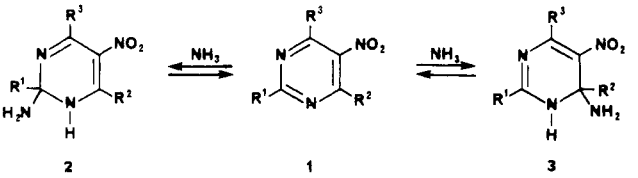
σ Adducts of 5-Nitropyrimidine with Ammonia. A solution of 5-nitropyrimidine (**1a**) in liquid ammonia was found to give, in the temperature range between −60 and −33 °C, two different σ adducts, i.e., **2a** and **3a** (Scheme II), as shown by NMR spectroscopy.

A. ^{1}H NMR Data. The ^{1}H NMR spectrum of a solution of **1a** in liquid ammonia at −60 to −40 °C recorded immediately after preparation of the solution consists mostly of two intense peaks at δ 8.18 (d, 2 H) and 5.33 (t, 1 H) with a small coupling constant J = 1.3 Hz (Figure 1a, Table I). A large upfield shift was found for the resonance signal of one of the protons of **1a** (Δδ 4.17) while the two other protons are shifted much less (Δδ 1.41). This result can only be explained if addition of ammonia to C-2 of

Scheme I



Scheme II



2 1 3

	R¹	R²	R³
a)	H	H	H
b)	H	D	D
c)	CH_3	H	H
d)	SCH_3	H	H
e)	C_6H_5	H	H
f)	CH_3SO_2	H	H
g)	H	OCH_3	OCH_3
h)	H	OCH_3	H

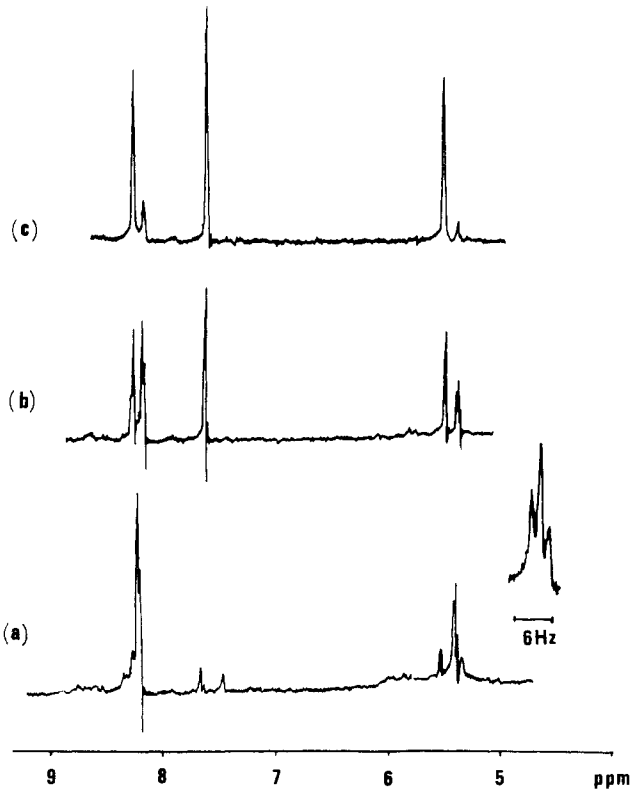


Figure 1. ^{1}H NMR spectra of 5-nitropyrimidine in liquid ammonia at −40 °C: (a) immediately after preparation of a solution, (b) after 15 min, (c) after 1 h.

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