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SYNTHESES OF METHYLENE-BRIDGED BENZOPYRENES, CARCINOGENIC COMPONENTS OF AUTOMOBILE EXHAUST RESIDUE

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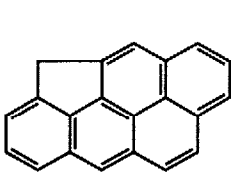
Abstract. Syntheses of the methylene-bridged derivatives of benzo[a]pyrene and benzo[e]pyrene (**1** and **2**) are described. The latter was obtained by a route involving in the key step tandem cyclization of a diacid derivative of pyrene. Although analogous preparation of **1** failed, it was obtained successfully by a synthetic route based on cyclopenta[def]phenanthrene.

Polycyclic aromatic hydrocarbons (PAHs) are widespread environmental pollutants present in urban air, auto exhaust, cigarette smoke, and many common foods.[1] Some of these PAHs, such as benzo[a]pyrene, are relatively potent carcinogens. Diol epoxide derivatives have been identified as their principal biologically active metabolites that bind covalently to DNA in mammalian cells.[2] Methylene-bridged derivatives of the PAHs benzo[a]pyrene and benzo[e]pyrene (**1** and **2**) have been tentatively identified as major components of the most carcinogenic fraction of automobile exhaust residue on the basis of UV and mass spectroscopic evidence.[3,4] Since alkyl substitution in the benzo ring that undergoes metabolic activation usually tends to abolish the tumorigenic activity of PAHs,[5] the nature of the active metabolites formed by these methylene-bridged PAHs is of considerable interest. Investigation of this problem has been hampered by the unavailability of **1** and **2** and the relative deficiency of methods for the synthesis of methylene-bridged PAHs.



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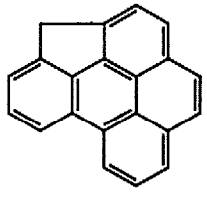
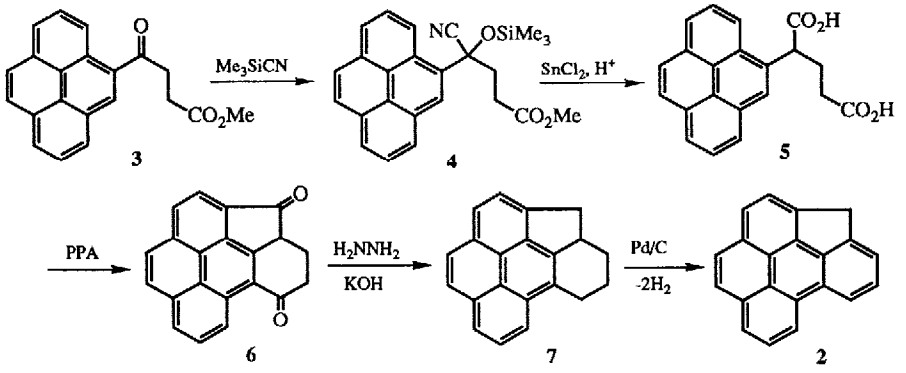


2

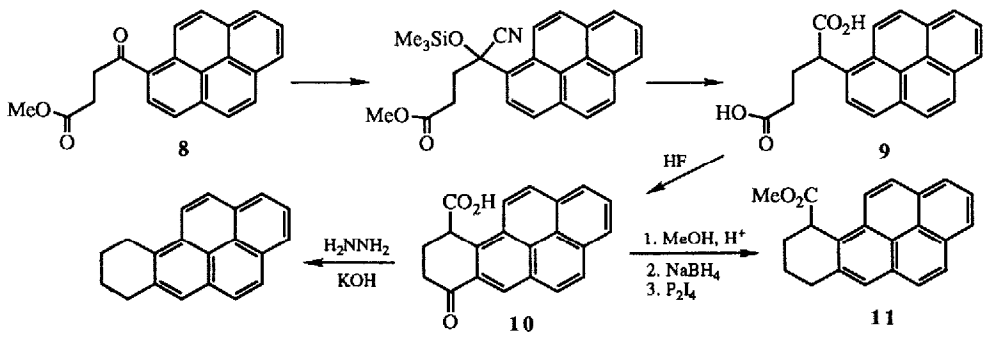
We now report convenient syntheses of both **1** and **2**. Synthesis of the latter was accomplished from methyl γ-oxo-4-pyrenylbutanoic acid (**3**) (Scheme I). This ketoester is readily available from 1,2,3,6,7,8-hexahydropyrene via succinoylation,[6] esterification, and aromatization with DDQ. Treatment of **3** with Me_3SiCN in refluxing benzene in the presence of a few drops of BF_3-etherate converted it to its trimethylsilyl cyanohydrin derivative (**4**). Reductive hydrolysis of **4** by $SnCl_2$ in hydrochloric-acetic acid[7] afforded cleanly the corresponding diacid **5** which on warming in neat polyphosphoric acid underwent tandem cyclization directly to the diketone **6**. Reduction of the latter by the Wolff-Kishner method furnished the partially saturated hydrocarbon **7**. Dehydrogenation of **7** over a 10% palladium/charcoal catalyst in refluxing triglyme yielded indeno[1,2,7,7a-cde]pyrene (**2**) as white platelets, mp 160-161(dec.)°C; the UV spectrum of **2** closely matched that reported.[4,8]

Scheme I



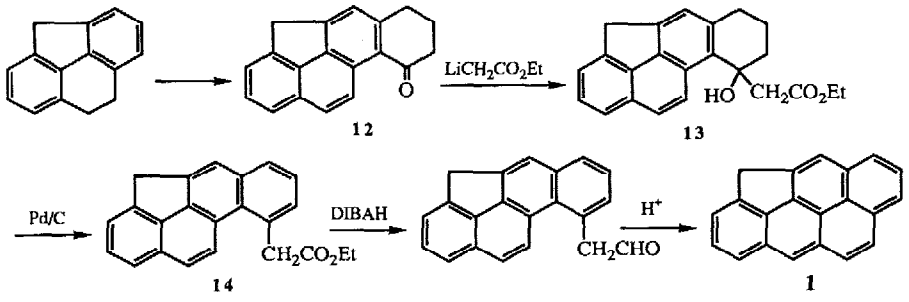
Attempted synthesis of the methylene-bridged benzo[a]pyrene analog **1** by appropriate modification of the same synthetic approach (Scheme II) was less satisfactory. The ketoester **8**, obtained from succinoylation of pyrene and esterification, underwent smooth conversion to the corresponding trimethylsilyl cyanide derivative on treatment with Me_3SiCN. Reductive hydrolysis of this adduct with the $SnCl_2$ reagent furnished the diacid **9**. Both steps afforded good yields (90%). However, attempted acidic cyclization of **9** in PPA, methanesulfonic acid, or other acids afforded generally intractable products. The sole exception was liquid HF from which there was obtained the keto-acid product **10** arising from cyclization to the 2-position of pyrene. This structural assignment was confirmed by Wolff-Kishner reduction of **10** which took place with decarboxylation to yield the known 7,8,9,10-tetrahydrobenzo[a]pyrene, mp 113-14°C (lit.[9] 113-14°C). When efforts to cyclize **10** directly failed, the carbonyl function was reduced in the hope of activating the polycyclic aromatic ring system for electrophilic substitution. Reduction was achieved in 60% overall yield by esterification followed by reaction with $NaBH_4$ and treatment of the resulting alcohol with P_2I_4.[10] However, attempted acid-catalyzed cyclization of the reduced ester (**11**), the free acid, or the corresponding acid chloride under a variety of conditions failed to yield the cyclized product. Resistance to cyclization is apparently a consequence of the relatively low susceptibility of the K-region positions of pyrene to electrophilic attack relative to the ease of other competing reactions.[11]

Scheme II



Synthesis of compound **1** was achieved via an alternative route based on 9,10-dihydrocyclopenta[def]-phenanthrene (Scheme III). The latter was obtained by hydrogenation of the parent hydrocarbon over a Pd/C catalyst and converted to the cyclic ketone **12** via Friedel-Crafts succinoylation, Wolff-Kishner reduction, dehydrogenation, and HF cyclization.[12] A two carbon extension was made from the carbonyl group of **12** by reaction with ethyl α-lithioacetate.[13] The unstable hydroxyester product **13** was dehydrogenated over a Pd/C catalyst in refluxing triglyme to yield the fully aromatic ester **14**. Reduction of **14** with diisobutylaluminum hydride in toluene furnished the corresponding aldehyde which was cyclized by treatment with methanesulfonic acid to yield indeno[1,2,7,7a-bcd]pyrene (**1**) as pale yellow plates, mp 204-205°C; the UV spectrum of **1** was essentially identical with that published.[8] The NMR spectrum of **1** was also in good agreement with this assignment, showing a characteristic two-proton singlet at δ 4.30 for the methylene protons.[14]

Scheme III



The foregoing syntheses provide the first synthetic access to the methylene-bridged derivatives of benzo-[a]pyrene and benzo[e]pyrene (**1** and **2**), making these compounds available for studies of their potential role as environmental carcinogens. The earlier tentative structural assignments of **1** and **2** made on the basis of their UV and mass spectral properties[4] are confirmed.

On the basis of the foregoing observations, it appears that synthetic routes to methylene-bridged PAHs that entail cyclization of a carboxylic acid intermediate, such as **5**,**9**,**10**, or **11**, to afford a five-membered ring are likely to be useful only in cases where the aromatic ring position undergoing reaction is relatively susceptible to electrophilic attack. Alternative synthetic approaches utilizing starting compounds that contain a preformed cyclopentano ring, such as cyclopenta[def]phenanthrene, appear inherently more attractive. The application of this type of synthetic approach to the preparation of several new methylene-bridged PAHs is currently in progress and will be reported in due course.

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Notes and References

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14. ^{1}H NMR (benzene-d_6) δ 4.30 (s, 2H, H_{10}), 7.61 (d, 1H, H_9, $J_{8,9}$ = 6.7 Hz), 7.79 (dd, 1H, H_8, $J_{7,8}$ = 8.1 Hz), 7.89-8.01 (m, 4H, $H_{2\text{-}5}$), 8.00 (s, 1H, H_{11}), 8.12 (d, 1H, H_7), 8.22 (d, 1H, H_1, $J_{1,2}$ = 7.8 Hz), 8.30 (s, 1H, H_6); UVmax (cyclohexane) nm 208 (ε 11 200), 260 (12 600), 287 (12 700), 299 (15 100), 355 (4 300), 373 (7 970), 394 (9 600); mass spectrum (EI) m/z 264 (M^+, 100%).

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