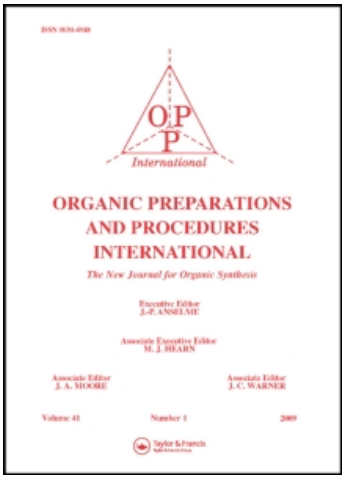

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THE LESS FAVORED 1-DERIVATIVES OF DIMETHYLDIHYDROPYRENE BY FORMYLATION

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9. Abbreviations used: Boc = *t*-butoxycarbonyl, Z = benzyloxycarbonyl, His = histidine.

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THE LESS FAVORED 1-DERIVATIVES OF DIMETHYLDIHYDROPYRENE BY FORMYLATION

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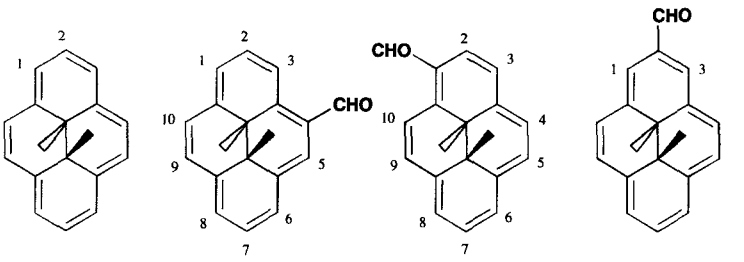
Dimethyldihydropyrene (**1**) is an interesting bridged [14]annulene which is an excellent probe for ring current effects.[1,2] Access to 1-substituted derivatives has been limited however, because electrophilic substitution, while extremely facile, proceeds at the 2-position.[3-5] For example, nitration, acetylation and benzoylation give 99%, 93% and 84% of the corresponding 2-derivatives, with no

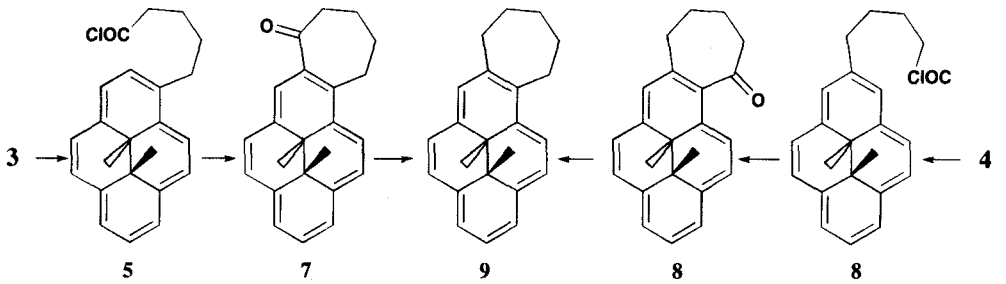
other products,[3] consistent with the relatively large stabilisation of the 2-cationic intermediate relative to the others, e.g. for nitration $\Delta H_f > 4$ kcal/mole.[4] Formylation, however, gives about 20% of a second



1 2 3 4

isomer,[5] whose structure was assigned as the 4-aldehyde (**2**) since on reduction to the supposedly 4-methyl compound, it gave identical UV and proton nmr spectra to a chiral sample prepared by the same authors using a different route. Its mp of 80-81° however, was not the same as the chiral sample, mp 110-115°. The low field proton nmr available at that time did not permit analysis of the aromatic region and hence thus could not lead to a certain assignment. Recently in our attempts to re-investigate the Mills-Nixon effect,[6] we required several cycloalkane fused dihydropyrenes. We used what we supposed was the 4-aldehyde (**2**) with unexpected results which led us to cast doubt on the original assignment. We now know that the minor isomer obtained on formylation of **1** is the 1-aldehyde (**3**). In the slightly more convenient procedure given below, this can now be obtained on a relatively large scale, repeatedly in 20% yield from **1** and dichloromethyl methyl ether using $TiCl_4$, together with 80% of the known[3] 2-aldehyde (**4**).

The structure of **3** follows unambiguously from its 360 MHz ^{1}H NMR spectra, with a COSY and NOESY analysis. Specifically, had the 4-aldehyde **2** been formed, a downfield singlet corresponding to H-5 of **2** would have been observed, together with a deshielded doublet for H-3. No singlet is observed, and instead the most deshielded aromatic proton is a doublet at δ 9.79 corresponding to H-10 of **3**. This shows a clear NOESY interaction (but no COSY) with the proton of the aldehyde, and is coupled (COSY) to H-9 which appears as a doublet at δ 8.76. Moreover, as expected for H-7 of **3**, only one shielded triplet at δ 8.11 is observed, whereas **2** would have shown two, corresponding to H-2 and H-7. H-2 of **3** is deshielded by the aldehyde to δ 8.66, with a clear COSY



5 7 9 8 8

coupling to H-3 and a NOESY interaction with the proton of the aldehyde. Only in the 1-aldehyde **3** should a NOESY interaction be seen between the aldehyde and H-2 and H-10.

Further unambiguous synthetic evidence is provided by separate extension of the aldehydes **3** and **4**, using a similar four-step sequence to that used to synthesize analogous cyclopentanone fused derivatives,[7] into the acid chlorides **5** and **6**. These after cyclization to the ketones **7** and **8**, followed by reduction, elimination and hydrogenation yield the same cycloheptane fused dihydropyrene **9**.[8] This mandates that the original isomeric aldehydes have adjacent formyl groups, and thus confirms the substitution position of **3**.

Pyrene itself undergoes electrophilic substitution at the 1-position and thus synthetically it is rather a challenge to obtain 2-derivatives.[9] The fact that dimethyldihydropyrene can be substituted at the 1- as well as the 2-position now opens up many synthetic avenues that were previously closed.

EXPERIMENTAL SECTION

Melting points were determined on a Reichert 7905 melting point apparatus integrated to a chrome-alumel thermocouple. NMR spectra were recorded on a Bruker AMX 360 using $CDCl_3$ as solvent and calibration peak. Mass spectra were obtained on a Finnigan 3300 gc-ms using methane for chemical ionization (CI). Evaporation was carried out at reduced pressure on a rotary evaporator. SiGel refers to Merck silica gel, 70-230 mesh.

Procedure for Formylation of Dimethyldihydropyrene (1).- Titanium tetrachloride (1.43 mL, 12.9 mmol) was added dropwise under N_2 to a solution of dimethyldihydropyrene **1**[10] (2.00 g, 8.62 mmol) in dry CH_2Cl_2 at 0°. α,α-Dichloromethyl methyl ether (1.01 mL, 11.2 mmol) (***Caution***: carcinogen) was added dropwise to this greenish-red solution, which then became blue-green, and this was stirred at 20 ° for 1.5 hr and then was added slowly to ice-water (250 mL). The organic layer was separated, and the aqueous layer further extracted with CH_2Cl_2, and the combined organic layers were dried ($MgSO_4$) and evaporated to yield a dark red gum, which was chromatographed over SiGel using dichloromethane-petroleum ether (1:25) as eluant. Eluted first was the green 1-formyl derivative **3**, 470 mg (20%), as green crystals, mp 109°, (lit.[5] mp 107-108°); ^{1}H NMR (360 MHz): δ 11.14 (s, 1, -CHO), 9.79 (d, J = 7.8 Hz, 1, H-10), 8.76 (d, J = 7.8Hz, 1, H-9), 8.70 (d, J = 7.5Hz, 1, H-4(5)), 8.67-8.63 (m, 5), 8.12 (t, J = 7.7Hz, 1, H-7), -4.03 and -4.07 (s, 3 each, $-CH_3$). ^{13}C NMR (90.6 MHz): δ 193.5, 138.7, 137.4, 137.1, 134.4, 127.4, 127.1, 126.6, 126.5, 126.4, 125.4, 124.2, 124.0, 122.7, 120.3, 31.0, 30.2, 14.2, 13.9. Eluted next was the red 2-formyl derivative **4**, 1.63 g (75%), as thin red plates from methanol, mp 129-130° (lit.[3] mp 131-132°), identical to a sample prepared as in reference 3. ^{1}H NMR (300 MHz): δ 10.58 (s, 1, -CHO), 9.03 (s, 2, H-1,3), 8.82 and 8.59 (AB, J = 8.0 Hz, 2 each, H-4,5,9,10), 8.54 (d, J = 8.0 Hz, 2, H-6,8), 8.20 (t, 1, H-7), -3.92 and -3.93 (s, 3 each, $-CH_3$); ^{13}C NMR (75.5 MHz): δ 193.6, 141.3, 139.6, 135.4, 128.9, 127.0, 124.9, 124.2, 31.5, 31.2, 15.7, 14.5.

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8. Both samples of **9** (obtained as an oily green wax) from the ketones **7** (red) and **8** (green) gave the same proton nmr spectra with internal methyl protons at δ -4.18 and -4.23 and exactly the same aromatic pattern (two AB q, one s, one AB_2) between δ 8.83 and 7.98 and the same mass spectra (CI MS) molecular ions at *m/z* = 301 (MH^+) consistent with $C_{23}H_{24}$. Full details of this and related sequences will be published elsewhere.

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