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BENZO[4,5]CYCLOHEPT[1,2,3-*bc*]ACENAPHTHYLENE AND BENZO[*a*]NAPHTH[3,4,4a,5-*cde*]AZULENE. NONALTERNANT ISOMERS OF BENZO[*a*]PYRENE

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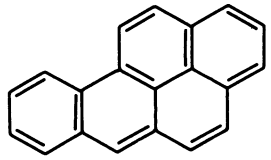
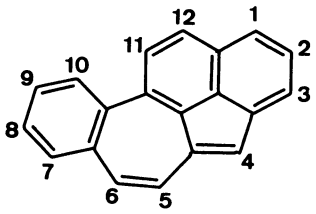
Summary : In order to examine the biological activities of the nonalternant isomers of potent carcinogen benzo[*a*]pyrene, benzo[4,5]cyclohept[1,2,3-*bc*]-acenaphthylene (2) and benzo[*a*]naphth[3,4,4a,5-*cde*]azulene (3), were synthesized. Some properties of 2 and 3 were also described.

Recently there has been considerable interest in understanding the mutagenic and carcinogenic activities of polycyclic aromatic hydrocarbons especially the potent mutagen and carcinogen benzo[*a*]pyrene (1).[1] Unlike alternant benzenoid hydrocarbons, the charge density distribution in nonalternant systems generally differ from unity.[2] Since the common feature unifying the structures of many chemical carcinogens is the electrophilic nature of the ultimate active species,[3] study on the biological activity of nonalternant versions of 1 is of particular interest.



(1)



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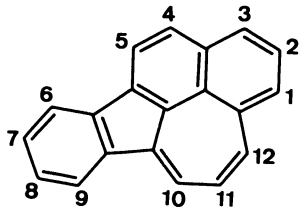


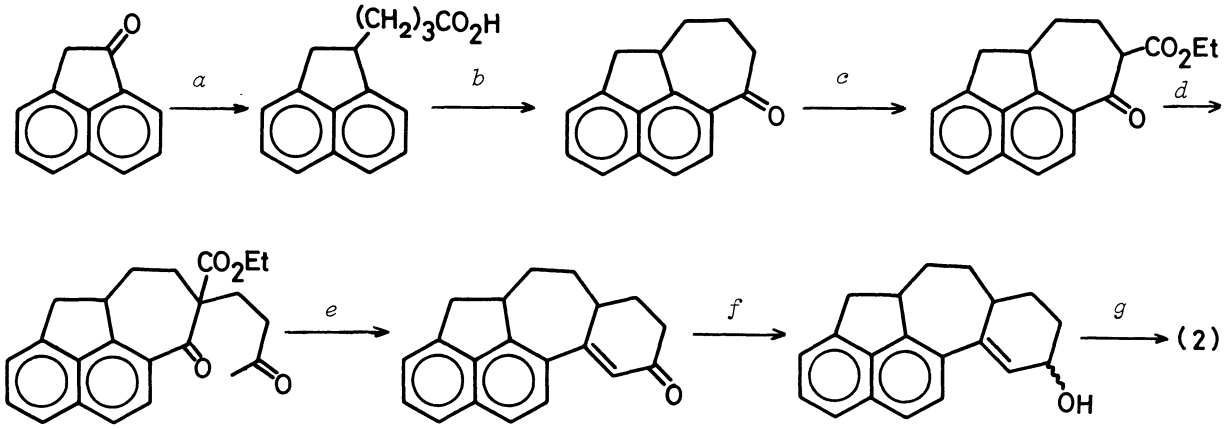
(3)

Such compounds synthesized to date are azuleno[1,2,3-*cd*]-,[4] azuleno[4,5,6-*cd*]-,[5] and azuleno-[5,6,7-*cd*]phenalenes,[6] and some of which exhibit strong mutagenicity.[7] We now wish to report the synthesis of the new nonalternant isomers of 1, benzo[4,5]cyclohept[1,2,3-*bc*]acenaphthylene (2) and benzo[*a*]naphth[3,4,4a,5-*cde*]azulene (3).

Our syntheses of 2 and 3 constitute stepwise construction of the corresponding carbon skeletons starting from 1-acenaphthenone[8] and γ-(9-fluorenyl)valeric acid,[9] respectively, and final dehydrogenation to the full conjugated systems. The sequence of the reactions, reagents, and reaction conditions used for the syntheses are shown in Chart 1 and 2.[10]

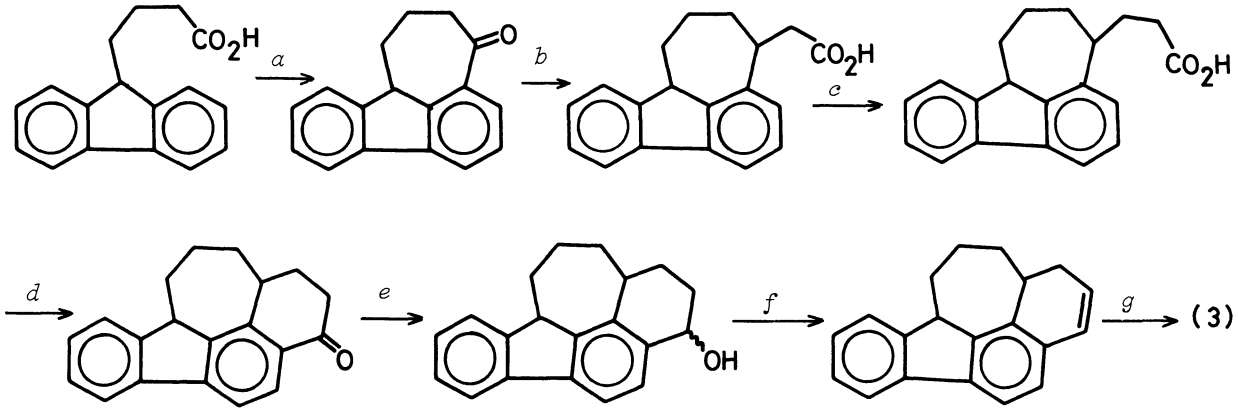
The compound 2 was obtained as thermally stable red plates of mp 137-139°C (from ethanol).

Chart 1.



a, (i) $BrCH_2CH=CHCO_2Et$/Zn-Hg in PhH-ether, reflux 24h; (ii) H_2/Pd(OH)$_2$-C in EtOH; (iii) KOH then H_3O^+; 17%; b, (i) PCl_5 in PhH, 0°C 30 min; (ii) $SnCl_4$ in PhH, 0-10°C 2h, 86%; c, NaH/$(C_2H_5O)_2CO$ in dioxane, reflux 5h, quant.; d, NaOEt/ $CH_3COCH_2CH_2\overset{+}{N}CH_3(C_2H_5)_2\ I^-$ in PhH, reflux 15 min then r.t. 24h, 96%; e, 45% aq KOH/CH_3OH, reflux 18h, 40%; f, $LiAlH_4$ in ether, r.t. 1h, 87%; g, S in trichlorobenzene, 210-220°C 45 min, 14%.

Chart 2.



a, H_3PO_4/P_2O_5, 95-100°C 2h, 30%; b, (i) $BrCH_2CO_2Et$/Zn-Hg in PhH-ether, reflux 20h, 83%; (ii) β-$C_{10}H_7SO_3H$ in PhH, reflux 1h, 88%; (iii) H_2/Pd(OH)$_2$-C in EtOH; 95%; (iv) KOH in H_2O-EtOH, reflux 2h, 95%; c, (i) $SOCl_2$, 80°C 1h, (ii) CH_2N_2 in ether; (iii) Ag_2O in CH_3OH, reflux 3.5h; (iv) KOH in EtOH, reflux 5.5h, then H_3O^+, 75%; d, (i) PCl_5 in PhH, reflux 25 min; (ii) $SnCl_4$ in PhH, 0-10°C 1h, 71%; e, $NaBH_4$ in EtOH, r.t. 24h, 97%; f, β-$C_{10}H_7SO_3H$ in PhH, reflux 1.5 min, 98%; g, DDQ in xylene, reflux 10 min, 75%.

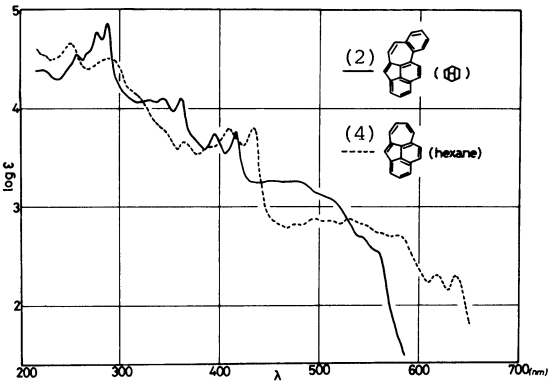


Fig. 1 Electronic Spectra of (2) and (4).

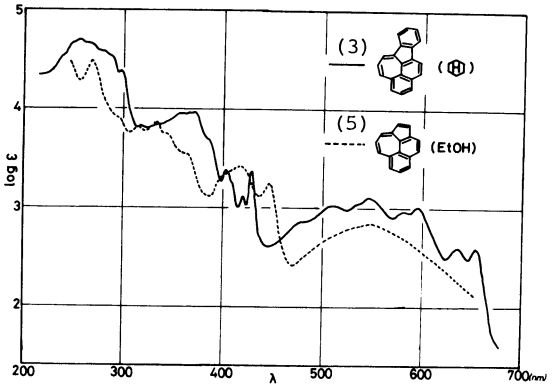
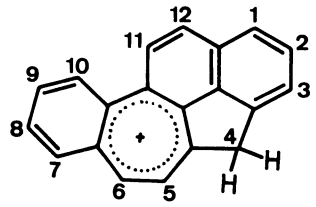


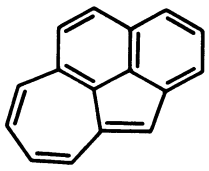
Fig. 2 Electronic Spectra of (3) and (5).

The ^{1}H-NMR spectrum of 2 showed two sets of AB-quartet at δ 7.11 and 7.37 (H-5,6, $J_{5,6}$=11.5 Hz) and δ 8.21 and 8.63 (H-11,12, $J_{11,12}$=8.9 Hz), one proton singlet of H-4 at δ 8.03, a broad doublet assignable to H-10 at δ 8.68 with $J_{9,10}$=9.5 Hz. Remaining protons, H-1,2,3,7,8, and 9, appeared as a complex multiplet at δ 7.48-8.15. As illustrated in Fig 1, the electronic spectrum of 2, [$\lambda_{max}^{cyclohexane}$ (nm, log ε): 223 (4.39), 258 (4.55), 277 (4.77), 287 (4.87), 329 (4.08), 344 (4.10), 361 (4.10), 395 (3.74), 416 (3.78), 453 (3.26), 478 (3.25), 542 (2.68)] exhibited a considerable blue shift compared with that of cyclohept[*bc*]acenaphthylene (4).[11] The compound 2 is a basic hydrocarbon and is reversibly protonated in degassed trifluoroacetic acid. The ^{1}H-NMR spectrum of this solution, δ 5.22 (s, 2H, H-4,4'), 9.02, 9.72 (AB-q, J=10.4 Hz, H-5,6), 9.14, 9.52 (AB-q, J=9.2 Hz, H-11,12), 9.78 (d, 1H, J=8.5 Hz, H-10), and 8.30-8.96 (m, 6H, H-1,2,3, 7,8,9), clearly indicates that the site of protonation was found to be 4-position as 2a. This behavior is consistent with the highest charge density at C-4 calculated by SCF-MO method.

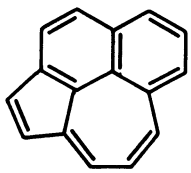
On the other hand, the alternate isomer 3 was isolated as black needles (dark purple in solution) of mp 177-178°C from hexane-benzene. Because of the lack of symmetry the complete assignments of the ^{1}H-NMR spectrum of 3 could not be made except protons attached to the seven-



(2a)



(4)



(5)

membered ring which constitute an ABX pattern at δ 7.47 (dd, J=7.6, 1.0 Hz, H-10), 7.21 (dd, J= 12.0, 1.0 Hz, H-12), and 6.44 (dd, J=12.0, 7.6 Hz, H-11). The remaining protons resonate at 7.4-

8.2 as a multiplet. Unlike 2, the electronic spectrum of 3, (Fig 2) λ_{max} (in c-hexane, nm, log ε): 256 (4.70), 286 (4.54), 298 (4.39), 318 (3.83), 357 (3.96), 365 (3.96), 372 (3.97), 403 (3.39), 419 (3.12), 429 (3.38), 509 (3.03), 546 (3.11), 581 (2.97), 595 (3.01), 636 (2.60), 654 (2.60), is closely similar to that of the parent cyclohepta[*klm*]benz[*e*]indene (5).[12] As would be expected from its structure, 3 is a nonbasic hydrocarbon.

Detailed examination of the mutagenicity of 2 and 3 are now in progress[13] and will be reported elsewhere. However, it is interesting to note that in the preliminary experiment the compound 2 was fairly strongly mutagenic to TA-100 in the absence of S-9 mix.

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References and Notes

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(13) Professor T. Sugimura and Dr. M. Nagao, National Cancer Center Research Institute, Tokyo, are currently engaged with the mutagenicity tests of 2 and 3.

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