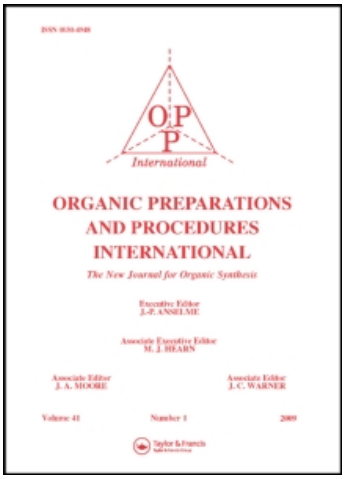

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CHO

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Dedicated to the memory of Professor R. Ken Forcé who passed away during the Summer of 1994.

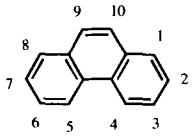
INTRODUCTION

Nitropolyarenes are ubiquitous genotoxic pollutants consisting of a polyarene nucleus with one or more nitro groups.[1,2] Certain nitropolyarenes, such as dinitropyrenes, are referred to as 'super' mutagens, owing to their exceptionally high mutagenic activities. There is compelling evidence that nitropolyarenes are formed either by electrophilic nitration in combustion processes or by radical nitration in the ambient air.[3,4] Intense analytical investigations in recent years[5-7] have resulted in the identification of more than 100 different mono- and di-nitropolyarenes from diesel particle samples. A possible etiologic role of nitropolyarenes in animal[8] and human cancers[9,10] has been suggested.

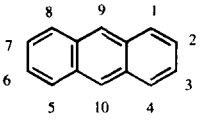
Current syntheses of nitropolyarenes are motivated by analytical and biological needs,[11] rather than theoretical interest as was the case in the early synthetic work.[12] This change in emphasis came about in 1978 when Pitts *et al*[13] demonstrated that polyarenes react with nitrogen oxides in a simulated environment to form highly mutagenic nitropolyarenes. The position of nitro substitution in nitropolyarenes governs its spatial orientation as respect to the aromatic moiety, its first half-wave reduction potential and other physicochemical properties, all of which are important for structure-activity-relationships of nitropolyarenes.[14] The strong-isomer dependence of the mutagenic activities of nitropolyarenes,[14] coupled with the recent identification of the 2-nitro derivatives of fluoranthene and pyrene as the major contaminants in the polluted air,[4,15] have necessitated the development of regiospecific preparation of a wide variety of nitropolyarenes.

This review will focus on papers dealing with nitropolyarene syntheses which appeared during the past 10 years (up to early 1994). Earlier accounts of this topic have been reviewed rather extensively by Ruehle *et al* in 1985.[11] The synthetic coverage of the present survey will be limited to the alternant or non-alternant nitropolyarenes containing three to five fused benzene rings and their oxygenated derivatives, as these are the compounds of major environmental and biological significance. Particular emphasis will be given to those of preparative synthetic utility; certain rare

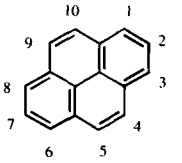
nitropolyarenes, which have been recognized based solely on the theoretical,[16] kinetic,[17,18] and limited spectroscopic data,[19] are not included. Also excluded are the nitro derivatives of alkyl-substituted and heterocyclic polyarenes.[20] The structures and the numbering systems of representative alternant polyarenes consisting of three to five fused benzene rings are shown in Fig. 1. The numbers in parentheses indicate the positions of nitro substitution for which compounds have been actually isolated and characterized.



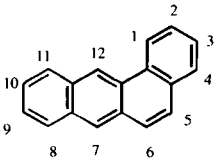
Phenanthrene
(1,2,3,4,9)



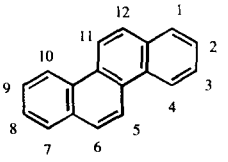
Anthracene
(1,2,9)



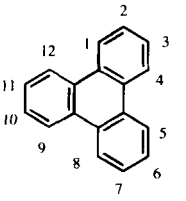
Pyrene
(1,2,4)



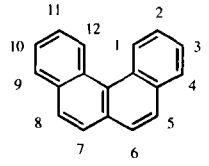
Benz[a]anthracene (BA)
(7,12)



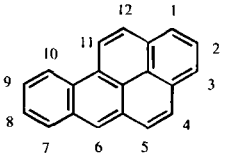
Chrysene
(1,2,3,4,5,6)



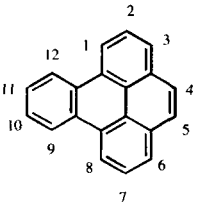
Triphenylene (1,2)



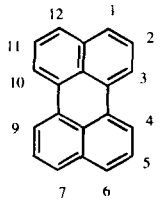
Benzo[c]phenanthrene (BcP)
(5)



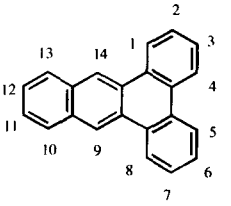
Benzo[a]pyrene (BaP)
(1,2,3,6)



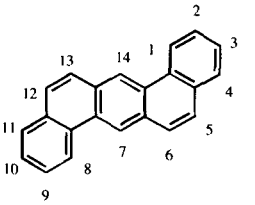
Benzo[e]pyrene (BeP)
(1,3,4)



Perylene
(1,3)



Dibenz[a,c]anthracene
(9)



Dibenz[a,h]anthracene
(3,5,7)

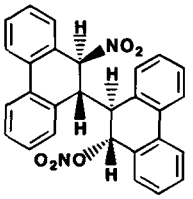
FIG. 1.

I. MONONITRATION OF ALTERNANT POLYARENES

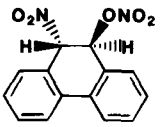
1. Tricyclic Polyarenes

a) Phenanthrene

There are five possible mononitro isomers for phenanthrene (Fig. 1). MO calculations predict the 9-position of phenanthrene to be the most reactive electrophilically, but other positions are within the limits of accuracy of the calculations.[21,22] Accordingly, the direct nitration of phenanthrene with HNO_3 at 0° furnished a 27:25:34 mixture of the 1-, 3- and 9-nitro isomers, which was difficult to separate.[21,23,24] Nitration with N_2O_5 in cyclohexane or chloroform furnished a substantial amount (8%) of the 4-nitro isomer instead of the 1-nitro isomer.[25] Treatment of phenanthrene with N_2O_4 in benzene gave 12% of dimeric **1** and 26% and 8% of *trans* (**2**) and *cis* (**3**) nitronitronates, in addition to a 8:9:37 mixture of the 1-, 3- and 9-nitro isomers.[26] Separation on chromatotron silica gel



1



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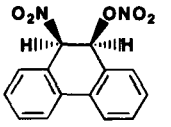

3

plate provided each individual mononitro isomer in pure state. It was found that **1** and **2** were thermally labile and decomposed under gas chromatographic conditions to phenanthrene and 9-nitrophenanthrene; therefore, special care needs to be exercised in using such technique for analyzing the N_2O_4 nitration products.[26] It should also be noted that an adduct similar to **2** has been proposed as a possible intermediate in the preparation of 2-nitrofluoranthene (N_2O_5/CCl_4) *via* an addition-elimination reaction.[27]

Independent syntheses of 1- and 4-nitrophenanthrene are available, but require multi-step synthetic sequences.[28,29] The relative easy synthetic access of the amino precursors[30] could make a direct oxidation approach an attractive alternative without the worry of separation. Oxidation of 1-aminophenanthrene *via* a diazonium salt procedure has been achieved in 60% yield.[29]

2-Nitrophenanthrene, which is unavailable by direct nitration, was obtained in excellent yield (91%)[31] by a modified procedure of Calder and Williams,[32] which consisted of a nitration of the commercially available **4** with N_2O_4 in CH_2Cl_2,[33] followed by DDQ dehydrogenation in benzene (Eq. 1). Chawla and Mittal[34] have reported the synthesis of 2-nitro isomer in 45% yield, *via* an interesting oxidative nitration at the least reactive 2-position of phenanthrene using silica gel-supported cerium (IV) ammonium nitrate.

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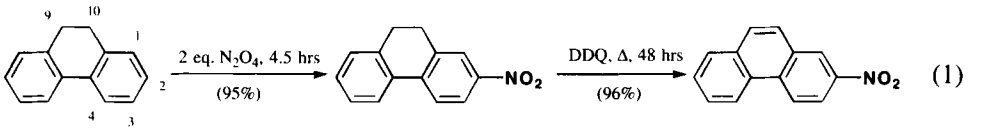
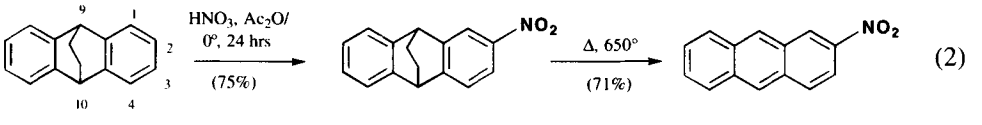


4 5 (1)

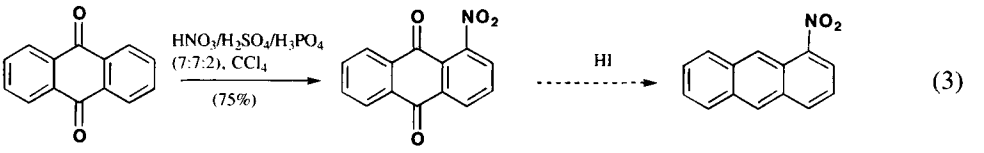
b) Anthracene

In accord with MO theoretical predictions, nitration of anthracene occurs exclusively at the meso 9-position with various nitrating agents.[35-37] Unlike the results with other polyarenes, the N_2O_4 nitration of anthracene also produced substantial amounts of 9,10-anthraquinone, suggesting the involvement of metastable primary products *via* a radical mechanism.[37] Under carefully controlled conditions, such adducts have been isolated in high yields and characterized as *cis*- and *trans*-9,10-dinitro-9,10-dihydroanthracene.[38]

2-Nitroanthracene, which is unavailable by direct nitration, was synthesized in 53% overall yield by nitration of 9,10-ethano-9,10-dihydroanthracene (**6**), followed by pyrolysis (Eq. 2).[39] This procedure appears to be a better route than that of Scribner and Miller,[40] which involved multiple



6 7 (2)



8 9 (3)

steps. The treatment of anthracene with an equimolar amount of HNO_3 in the presence of graphite bisulfate gave 1-nitroanthracene in 62% yield directly.[41] Alternatively, the 1-nitro isomer was obtained by direct oxidation of 1-aminoanthracene with $NaNO_2$ in aqueous acetonitrile.[42] A similar conversion may be possible for the 2-amino isomer, which is also commercially available. A recent high yielding synthesis of 1-nitroanthraquinone (**9**)[43] is of special interest, since it can be conveniently reduced to the 1-nitro isomer by a well known HI reduction procedure (Eq. 3).[44]

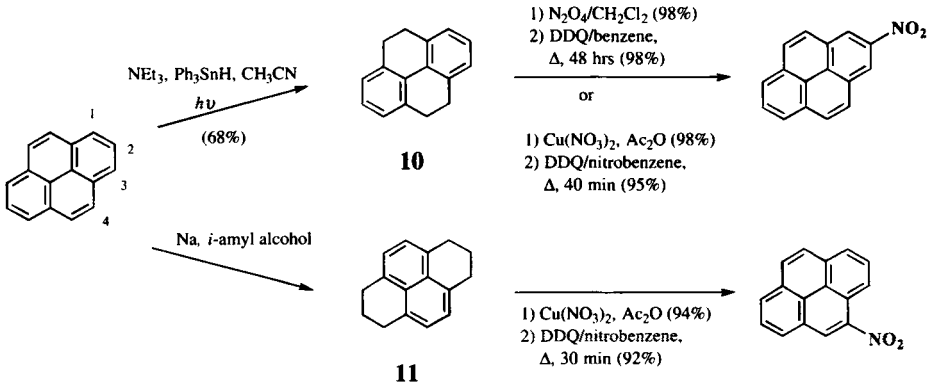
2. Tetracyclic Polyarenes

a) Pyrene

Three mononitro isomers (1-, 2- and 4-) are possible for pyrene due to its highly symmetric nature (Fig. 1). 1-Nitropyrene is a prototype environmental nitropolyarene pollutant and is the major component in combustion processes, whereas the 2-nitro isomer is detected in the ambient air.[3,4]

Although the environmental existence of 4-nitropyrene has not been documented, it is among the most mutagenic and carcinogenic of the nitropolyarenes.[45]

A clean conversion of pyrene into 1-nitropyrene was achieved through a nitration with either N_2O_4 in CH_2Cl_2[31] or sodium nitrite-peroxydisulfate in acetonitrile.[46] The latter is an oxidative nucleophilic aromatic substitution reaction involving sodium peroxydisulfate as the oxidizing agent and nitrite anion as the nucleophile.[46] Both nitrations proceeded almost quantitatively with minimum contamination of unreacted pyrene or dinitropyrenes. Under carefully controlled temperature and concentration of HNO_3, Fatiadi and Hilpert[47] were able to obtain pure (99.8%) 1-nitropyrene in 85% yield and its perdeuterated analog with high isotopic purity (99.44 atom %) in 75% yield.



Scheme 1

Bolton's original synthesis of 2-nitropyrene,[48] which involves a nitration of the tetrahydropyrene **10**, followed by aromatization, is still the method of choice (Scheme 1). A great improvement of overall yields (>93%) was achieved by using N_2O_4/CH_2Cl_2[31] or $Cu(NO_3)_2/Ac_2O$[46] as nitrating systems and DDQ as an oxidizing agent. The use of nitrobenzene as refluxing solvent expedites the DDQ oxidation, otherwise a slow process due to the presence of the electron-withdrawing nitro group.[46] The tetrahydro starting material **10** has been prepared by a photochemical reduction using triphenyltin hydride as hydrogen donor[46] and this procedure was found to be superior to the conventional metal hydrogenation methods,[49] which often result in mixtures of hydrogenated products.

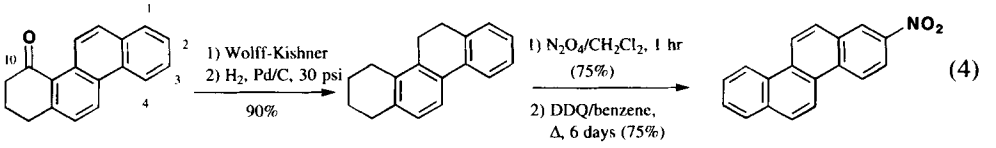
Following the original procedure of Bavin,[50] 4-nitropyrene was prepared in excellent (87%) overall yield by nitration of the hexahydropyrene **11** with $Cu(NO_3)_2$ in acetic anhydride, followed by a DDQ dehydrogenation in nitrobenzene (Scheme 1).[46]

b) Chrysene

All six possible mononitrochrysenes have been prepared by a combination of direct and indirect approaches.[24,51,52] Direct nitration of chrysene with N_2O_4 in CH_2Cl_2 takes place at the 6-position exclusively (>97%).[33] Svendsen *et al* [24] have shown the presence of at least five mononitrochrysenes by the HPLC analysis of a HNO_3 nitration mixture modified after the procedure of Dewar *et al.*[51] Aside from the major 6-nitrochrysene, spectroscopic and chromatographic evidence have been

CHO

presented for the presence of the 4- and 5-isomers as minor products. Two remaining coeluting peaks were tentatively assigned as 1- and 3-nitrochrysene. 2-Nitrochrysene, which is unobtainable *via* direct

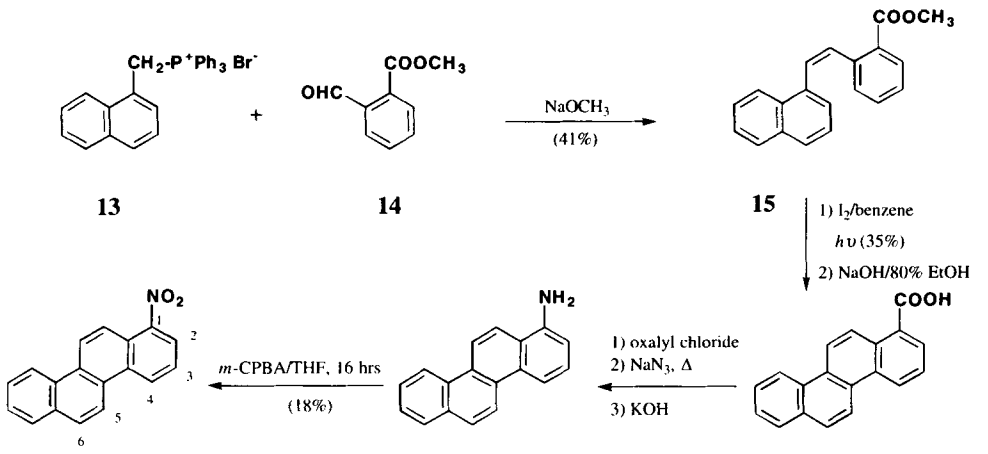


(4)

12

nitration, was prepared in 56% yield through an indirect approach, consisting of nitration of hexahydrochrysene (**12**) and a subsequent aromatization (Eq. 4).[31]

1, 2 and 3-Nitrochrysene have also been prepared by oxidation of the corresponding aminoarenes, which were in turn prepared *via* a multi-step total synthesis.[52] Scheme 2 illustrates the synthesis of 1-nitrochrysene as an example. Condensation of the naphthyl phosphonium salt **13** with 1-carbomethoxy-benzaldehyde (**14**) yielded an olefinic adduct **15**, which was cyclized photochemically and hydrolyzed to give 1-chrysenecarboxylic acid (**16**). The acid **16** was then transformed into the amine derivative **17** *via* a Curtius rearrangement, followed by base hydrolysis. The overall yield of **17** from **14** was about 5%. Using appropriate analogs of **14**, 2- and 3-aminochrysene were prepared in 16 and 14% yields, respectively. 4- and 5-Aminochrysene were prepared similarly starting from the 4- and 5-carbomethoxy derivatives of **16**, respectively. Only three (1-, 2- and 3-) of the above five aminochrysenes were oxidized with *m*-CPBA to the corresponding nitropolyarenes in acceptable yields (18-30%). Steric hindrance was suggested as the possible cause for the resistance of 4- and 5-aminochrysene towards oxidation.[52]



13 **14** **15** **16** **17**

Scheme 2

c) Benz[a]anthracene (BA)

Newman and Lilje[53] reported the synthesis of 7-nitro-BA in 55% yield by direct nitration of BA with HNO_3 in CH_2Cl_2. Iversen *et al*[54] identified five additional mononitro isomers from a nitration mixture prepared similarly with acetyl nitrate (HNO_3/Ac_2O). The two major products formed in an 11:4 ratio were assigned as 7- and 12-nitro-BA, respectively, on the basis of ^1H NMR and mass spectral analyses. The remaining four isomers, which were formed in very low yields, were suggested to be the 5-, 6-, 8- and 11-nitro isomers based on mass, electron densities and length/breadth data.[19] Under simulated solid state photolysis conditions, both 7- and 12-nitro isomers were oxidized exclusively into the 7,12-quinone, along with small amounts of phenols.[55]

d) Triphenylene

Highly symmetric triphenylene can have only two (1- and 2-) nitro isomers (Fig. 1). The reactive site in triphenylene is predicted to be the sterically crowded 1-position.[56] However, the available experimental results on the electrophilic substitution of triphenylene are not clear: thus, while chlorination and deuteration favored 1-substitution as predicted, bromination, sulfonation and acylation afforded exclusively 2-substituted products.[57] Direct nitration of triphenylene with acetylnitrate furnished an approximately equal mixture of the 1- and 2-nitro isomers in moderate yields (46-59%).[24,56,58] According to a comparative nitration study by Radner,[33] the N_2O_4 nitration of triphenylene in CH_2Cl_2 occurred predominantly (78%) at the less hindered but less reactive 2-position, whereas a small excess of 1-nitro isomer (55%) was obtained with acetyl nitrate, which suggested the involvement of a different nitration mechanism. Addition of catalytic amount of methanesulfonic acid greatly facilitated the N_2O_4 reaction, without altering the isomer distribution. Extensive HPLC purifications were required to separate the two isomers.[24]

e) Benzo[c]phenanthrene (BcP)

Nitration of BcP gave the 5-nitro isomer in 54% yield, plus two unknown dinitro derivatives.[59] While this is the only reported nitration of BcP, Newman and Blum[60] reported the synthesis of all six possible amino derivatives, which could be converted to nitro compounds by direct oxidation. During recent years much attention has been focused on BcP as a consequence of the exceptionally high tumorigenicity exhibited by its fjord-region diol epoxides.[61]

3. Pentacyclic Polyarenes

a) Benzo[a]pyrene (BaP)

Direct nitration of BaP afforded the 6-nitro isomer as the major product, along with a mixture of the 1- and 3-isomers (<16%).[51,62,63] Unlike the results with other polyarenes,[33] the treatment of BaP with an equimolar amount of N_2O_4 produced significant amounts of undesired dinitro isomers.[64] Thus, it was necessary to use a half equivalent of N_2O_4 to ensure mononitration.[64] To maximize the formation of 1- and 3-nitro-BaP, an indirect nitration route was sought.[65] It was reasoned that nitration of the tetrahydro-BaP **18**, which contained a pyrene moiety, would take place conformably at the three positions (1, 3 and 6). As expected, the nitration of **18** with $AgNO_3$/TFA in acetic anhydride occurred equally at the 1-, 3- and 6-positions (**20**, **21** and **19**, respectively), which

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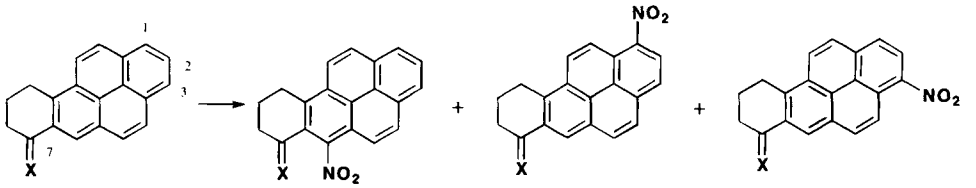
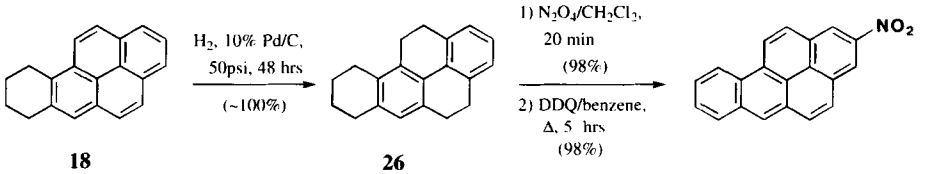


18: X = H_2 **19**: X = H_2 (36%) **20**: X = H_2 (28%) **21**: X = H_2 (31%)

22: X = O **23**: X = O (22%) **24**: X = O (35%) **25**: X = O (30%)

after separation and aromatization afforded the desired nitro-BaPs.[65] When commercially available 7-keto-BaP **22** was employed instead of **18**, the relative yield of the 1-nitro isomer (**24**) was increased by 7%, whereas that of 6-nitro isomer (**23**) decreased by 14%, apparently due to the deactivating effect of the 7-keto group.[66] The use of the N_2O_4/CH_2Cl_2 nitrating system[67] gave an even higher regioselectivity (41%) of **24** and was found to be superior to the acid catalyzed nitrating systems (*e.g.*, HNO_3 or $NaNO_3$/TFA/Ac_2O), which produced considerable amounts of dinitro and quinone byproducts that caused difficulties in purification.



18 **26** (5)

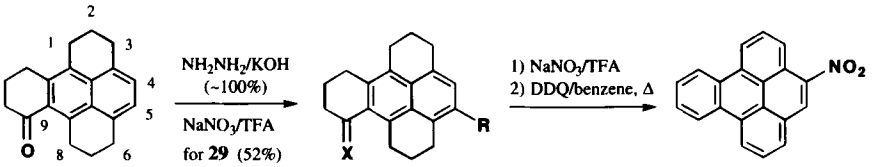
As with other 2-substituted nitropolyarenes described earlier, 2-nitro-BaP was synthesized by nitration of **26**, followed by dehydrogenation (Eq. 5).[31] The octahydro-BaP **26** contains a biphenyl ring system, in which all the reactive 2-positions of biphenyl moiety are blocked. Therefore, the nitration must occur at the 2-position of BaP, which is the only available 4-position. Fu *et al*[68] have synthesized several (4-, 11- and 12-) amino derivatives of BaP, which may be oxidized directly to yield their nitro derivatives.

b) Benzo[e]pyrene (BeP)

The electrophilic reaction pattern of BeP is known to resemble closely that of pyrene.[57] BeP was nitrated with 3 eq. of HNO_3 to yield an equal mixture of the 1- and 3-nitro isomers in 80% yield, whereas the nitration with a large excess (10 eq.) of HNO_3 increased the relative distribution (>64%) of 1-nitro-BeP in a better yield (93%).[62] The preferential nitration at the sterically hindered 1-position of BeP under less discriminating conditions was noted. Nitration with $NaNO_3$/TFA in acetic anhydride also furnished a mixture of the two isomers.[69] Due to the unique perpendicular orientation of the nitro substituent to the aromatic ring, the bay-region H12 resonance of 1-nitro-BeP was shielded significantly (~0.6 ppm) as compared to BeP.

4-Nitro-BeP was prepared in three steps, consisting of Wolf-Kishner reduction of **27** and nitration (**28**), followed by dehydrogenation (Eq. 6).[69] Interestingly, the direct nitration ($NaNO_3$/TFA) of **27** took place regiospecifically at the 5-position (*e.g.*, **29**), not at the 4-position.[70] Nonetheless, **29**

could be eventually converted to the 4-nitro-BaP *via* a reduction/dehydration/dehydrogenation sequence.



27 **28**: X = H_2, R = H

29: X = O, R = NO_2

c) Perylene

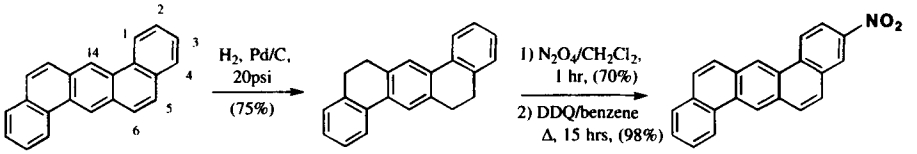
Treatment of perylene cation radical with nitrite ion ($AgNO_2/I_2$ in acetonitrile) resulted in a rapid and exclusive mononitration at the 3-position.[71] The nitration with 0.75 molar equivalent of N_2O_4 in CH_2Cl_2 was completed in one minute (95%) with a less than 1% contamination with the 1-nitro isomer.[33] On the other hand, the same reaction in the low ionizing solvent CCl_4 yielded a 35:62 mixture of the 1- and 3-isomers in an excellent yield (97%), suggesting the involvement of a different reaction mechanism.[72] Eberson and Radner,[72] and others[73] have shown that the nitration of perylene using a variety of HNO_3 nitrating conditions gave the 3-isomer as the major product, with only at best 5% of the 1-nitro isomer. These results contrasted a previous report by Looker,[74] who obtained a substantial amount (24%) of the 1-nitro isomer when using HNO_3 in dioxane. Nonetheless, the two isomers were readily separated by column chromatography and characterized by ^1H NMR.[74]

d) Dibenz[a,c]anthracene

Nitration of dibenz[a,c]anthracene with acetyl nitrate at 50° gave three mononitro isomers, of which the major product was identified as the 9-nitro isomer based on ^1H NMR and MS analyses.[54] The two minor products were suggested to be the 10- and 11-nitro isomers, based on electron density calculations.[19] The nitration with $NaNO_3$/TFA in acetic anhydride also provided 9-nitro isomer as the major product.[75]

e) Dibenz[a,h]anthracene

Nitration of dibenz[a,h]anthracene with acetyl nitrate afforded the 5- and 7-nitro isomers in a ratio of 4:19.[54,19] The presence of small amounts of the 6-nitro isomer was also suggested. The nitration with $NaNO_3$/TFA in acetic anhydride afforded the 7-nitro isomer as well.[75] The synthesis of the 3-nitro isomer, in which the nitro group is located on the longest axis of the molecule, was achieved in 69% overall yield by a N_2O_4 nitration of the tetrahydro **30** followed by dehydrogenation (Eq. 7).[31]



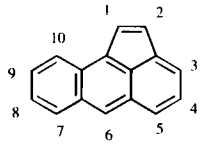
30

CHO

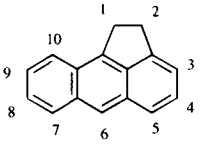
II. MONONITRATION OF NON-ALTERNANT POLYARENES

1. Aceanthrylene and Aceanthrene

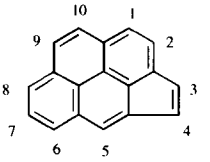
Mulder *et al*[75] have prepared and characterized nine of the ten mononitro isomers of aceanthrylene and its dihydro derivative, aceanthrene (Fig. 2).



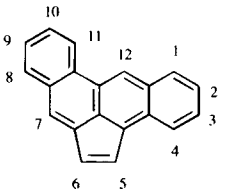
Aceanthrylene
(2,3,4,5,6,7,8,9,10)



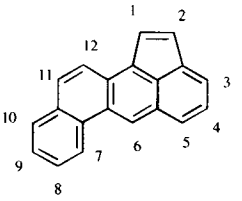
Aceanthrene
(1,3,4,5,6,7,8,9)



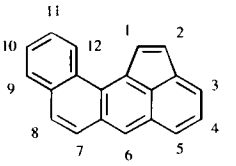
Cyclopenta[cd]pyrene (CPP)
(1,2,4,5,6,7,8,9)



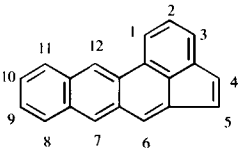
Benz[e]aceanthrylene
(6)



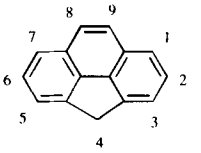
Benz[j]aceanthrylene
(2)



Benz[l]aceanthrylene
(2)



Benz[k]aceanthrylene
(4,5)



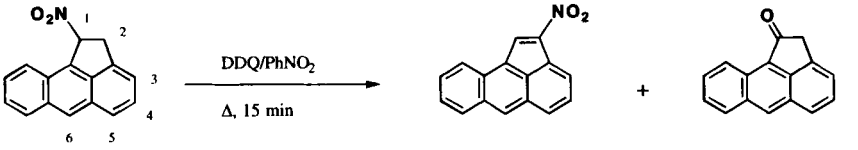
4*H*-Cyclopenta[def]phenanthrene
(1,2,3,8)

FIG. 2

Structures and Numbering System of cyclopenta-fused polyarenes. The numbers in parentheses indicate the positions of nitro substitution for which compounds have been synthesized and characterized.

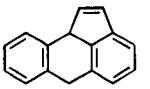
Direct nitration of aceanthrylene with N_2O_4/CCl_4 afforded 2-nitroaceanthrylene as the single major product (55%). Attempts have also been made to prepare the 1-nitro isomer. In one approach, the treatment of 1-nitroaceanthrene (**31**) with DDQ in refluxing nitrobenzene resulted in an unexpected rearrangement to the 2-nitro isomer (**32**) and the ketone **33** (Eq. 8). The starting material **31** was prepared as the major product (36%) in the N_2O_4 nitration of aceanthrene. In another attempt, the partially hydrogenated analog **34** was nitrated with mild nitrating agent, $AgNO_3/NaNO_2/I_2$ in acetonitrile, in the hope that the substitution would occur regiospecifically at the β-position of the conjugated

double bond (*e.g.*, 1-position of **34**).[77] Instead, it produced a complex mixture, of which only trace amounts of **32** could be identified. They also attempted to prepare 2-nitroaceanthrene by reducing the etheno double bond of 2-nitroaceanthrylene (**32**) using $NaBH_4$, but the nitro group was reduced instead.



(8)

31 **32** **33**

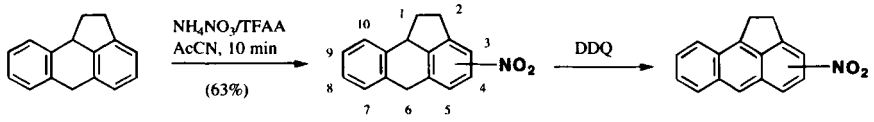


34

6-Nitroaceanthrylene was prepared in 45% yield by HNO_3 nitration of the 1-keto derivative (**33**) and subsequent reduction/dehydration.

Since the other positions are not sufficiently reactive for direct nitration, indirect approaches involving nitration of partially hydrogenated aceanthrylenes, followed by aromatization, have been necessary. Nitration of the tetrahydro analog **35** with NH_4NO_3/TFAA in acetonitrile gave a 1:1:3:3 mixture of the 3-, 4- and 5-nitro derivatives (**36**, **37** and **38**) in 63% overall yield, which after separation and dehydrogenation with 1 eq. of DDQ afforded the corresponding nitroaceanthrenes (Eq. 9). A further DDQ dehydrogenation furnished the nitroaceanthrylene derivatives as the final products. As anticipated, the nitration took place in the more substituted aromatic ring of **35**.

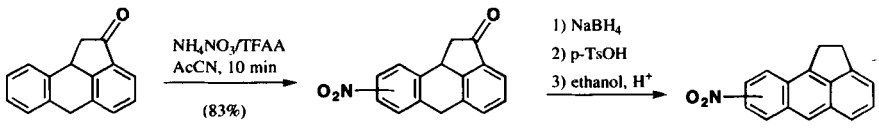
For the preparation of derivatives containing one nitro group at positions 7, 8, 9, or 10, the ketone **39** was utilized as the starting material (Eq. 10). The strategy was based upon the belief that



(9)

35

36: 3-NO2
37: 4-NO2
38: 5-NO2



(10)

39

40: 7-NO2
41: 8-NO2
42: 9-NO2
43: 10-NO2

CHO

the 2-keto group of **39** would deactivate the adjacent aromatic ring, thus allowing the nitration to occur in the terminal benzo ring. Indeed, nitration with NH_4NO_3/TFAA in acetonitrile yielded a 4:4:4:1 mixture of the four expected isomeric nitro ketones (**40**, **41**, **42** and **43**) in 83% yield. The nitroketone mixture was reduced, dehydrogenated and isomerized to give nitroaceanthrenes, which could be partially separated. A final aromatization provided the corresponding nitroaceanthrylene derivatives.

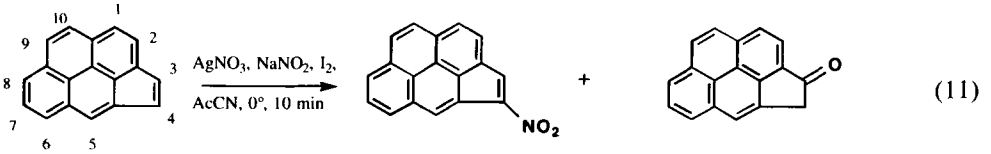
2. Cyclopenta[cd]pyrene (CPP)

The ubiquitous carcinogen CPP is probably the most studied cyclopenta-fused polyarene. In a manner similar to the foregoing examples of aceanthrylene, seven of nine possible mononitro isomers have been prepared (Fig. 2).[78]

Direct nitration of CPP with $AgNO_3/NaNO_2/I_2$ in acetonitrile took place at the electron rich 4-position (**44**) in moderate yield (43%), but a considerable amount (30%) of the ketone **45** was also formed (Eq. 11).[79] Nitration with strongly acidic HNO_3 was found to cause serious degradation of CPP, probably due to its highly reactive etheno bridge. Exclusive formation of 4-nitro-CPP was obtained with N_2O_4 in CH_2Cl_2.[80]

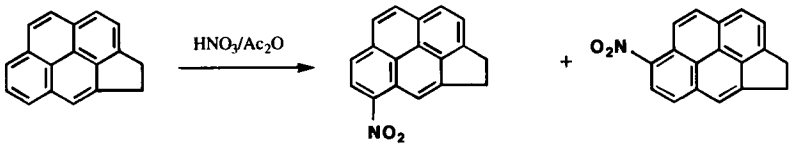
Four partially saturated CPP-derivatives containing the pyrene (**46**), phenanthrene (**49** and **52**) and biphenyl (**53**) moieties were individually nitrated and aromatized to obtain the remaining nitro isomers.[78] Treatment of **46** with less than 1 eq. of acetyl nitrate (HNO_3/Ac_2O) yielded about equal amounts of 6- and 8-nitro-CPP (**47** and **48**) as the only detectable mononitro products, which were separated by means of HPLC (Eq. 12). Under similar conditions, however, Minabe *et al*[81] isolated substantial amounts (~10%) of an equal mixture of the 1- and 5-nitro isomers, in addition to **47** and **48** (24 and 21%, respectively). Nitration of the 3-keto-CPP (*e.g.*, **45**) gave a similar reaction profile, but lacked 5-nitro-CPP.[81]

The nitration of **49** with acetyl nitrate resulted in complicated oxidative reaction mixtures, including the loss of a cyclopenta ring, as evidenced by the formation of 1-nitropyrene.[78] Despite its low reactivity, nitration with $Cu(NO_3)_2/Ac_2O$ gave cleaner products with a mixture of 1- and 9-nitro-CPP (**51** and **50**) and a small amounts of 8-nitro-CPP, in addition to the recovered starting material, CPP (54%)(Eq. 13). The nitration of **52** and **53** proceeded to similar extents with $Cu(NO_3)_2/Ac_2O$ to furnish exclusively the 5- and 2-nitro isomers, respectively.



43% 30%

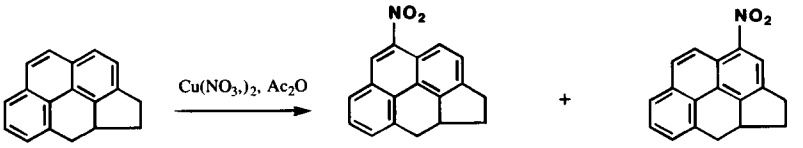
44 **45** (11)



(12)

29% 28%

46 **47** **48**



(13)

29% 16%

49 **50** **51**

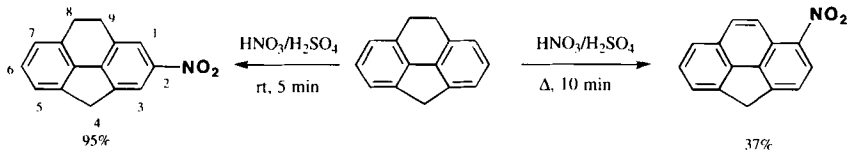
52 **53**

3. Cyclopenta-fused Benz[a]anthracenes

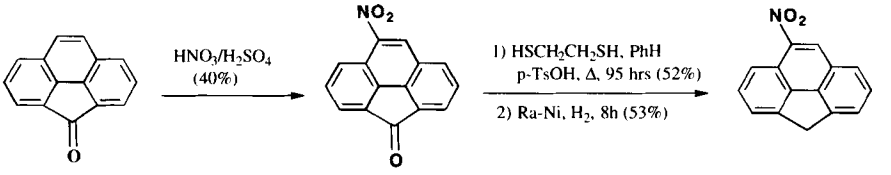
Goldring *et al*[80] have carried out the N_2O_4 nitration of four cyclopenta-fused derivatives of benz[a]anthracene (Fig. 2): benz[e]aceanthrylene, benz[j]-aceanthrylene, benz[l]aceanthrylene and benz[k]aceanthrylene. As expected, the nitro substitution took place preferentially at the electron rich etheno bridge to give single mononitro isomers at the 6-, 2-, 2- and 4-positions, respectively. In case of benz[k]aceanthrylene, the 5-nitro isomer was also formed in equal amounts.

4. 4*H*-Cyclopenta[def]phenanthrene (Fig. 2) is a prototype methylene bridged polyarene and the nitration with HNO_3 in nitromethane gave a mixture of the 1- (20%), 3- (4%) and 8-nitro (6%) isomers, along with a trace of the 2-nitro isomer.[82] A substantial amount (~8%) of the 2-nitro isomer was obtained if acetic anhydride was used as a solvent. This preferential 1-nitro substitution contrasted with the predominant 9-substitution in phenanthrene. Nitration of the 8,9-dihydro analog **54** with HNO_3/H_2SO_4 at room temperature for 5 min afforded exclusively the 2-nitro isomer **55** (95%)(Eq. 14). Interestingly, however, the same reaction under refluxing for 10 min provided a fully aromatized 1-nitro isomer **56** as the major product (37%)(Eq. 14). The 8-nitro isomer was independently prepared by nitration of the 4-keto analog **58**, followed by a thioketalization/reduction sequence (Eq. 15).[82] The deactivating effect of the 4-keto function caused nitration to occur at the 8-position.

CHO



55 54 56 (14)



58 59 (15)

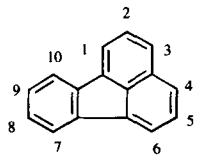
5. Fluoranthene (Fig. 3) is one of the more abundant environmental contaminants. All five possible mononitrofluoranthenes (1-, 2-, 3-, 7- and 8-) and some dinitro derivatives are found in the environment and exhibit different mutagenicities.[83,84]

Theoretical calculations predict that the most reactive site of fluoranthene is the 3-position and the least reactive is the 2-position (3>7>8>1>2) in the electrophilic substitution reaction.[22,85] Experimental data with various nitrating agents appear to be in good accord with this prediction. The two major products, the 3- and 8-nitro isomers, which account for more than 70% of the total, were readily isolated either by column chromatography or recrystallization from the direct nitration mixture.[85,86]

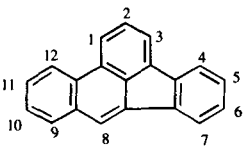
Alternate access to 1- and 7-nitrofluoranthene was desirable because of the difficulty of isolating them from direct nitration mixtures. A new synthesis of the 1-nitro isomer by van Haeringen *et al*[86] entails a regioselective nitration of 2,3-dihydrofluoranthene (**60**) with NH_4NO_3/TFAA in acetonitrile, followed by aromatization with DDQ (Eq. 16). The new procedure appears to provide cleaner nitration products, while affording a yield (~20%) comparable to the previous procedure of Dewar and Michl.[87]

The ketone **61** was utilized as the key starting material for the preparation of 7-, 8- and 2-nitrofluoranthene (Scheme 3).[86] Strong deactivation of the 3-keto functionality and the directing effect of the fluorene moiety of **61** cause the direct nitration to take place at the 7- and 9-positions, affording a 2:3 mixture of **62** and **63** in moderate yield (41%). After separation on silica, they were transformed into the corresponding nitrofluoranthenes *via* a reduction/dehydration/aromatization sequence. The same ketone **61** was reduced with sodium borohydride and dehydrated to give **64** in 91% yield. As anticipated,[77] the nitration of **64** with $AgNO_2/I_2$ in acetonitrile occurred regioselectively at the β-position (*e.g.*, 2-position of fluoranthene) of the conjugated double bond (Scheme 3). It was fortuitous that the subsequent dehydrogenation also took place under the nitration conditions, affording the target

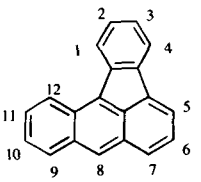
compound in one step (32%). The use of regular nitrating agents resulted in nitro-substitution in the aromatic moiety of the molecule.



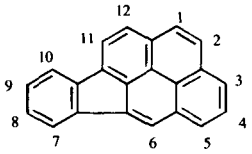
Fluoranthene
(1,2,3,7,8)



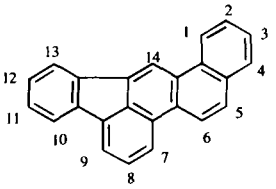
Benz[e]acephenanthrylene
(1,8)



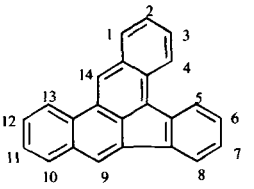
Benz[a]aceanthrylene
(8)



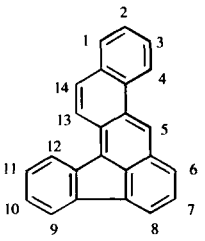
Indeno[1,2,3-cd]pyrene
(12)



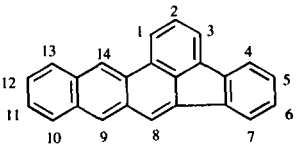
Indeno[1,2,3-hi]chrysene
(5)



Dibenz[a,e]aceanthrylene
(14)



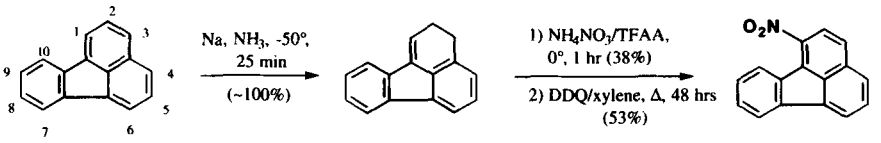
Dibenz[a,j]aceanthrylene
(5)



Benz[e,k]acephenanthrylene
(9)

FIG. 3

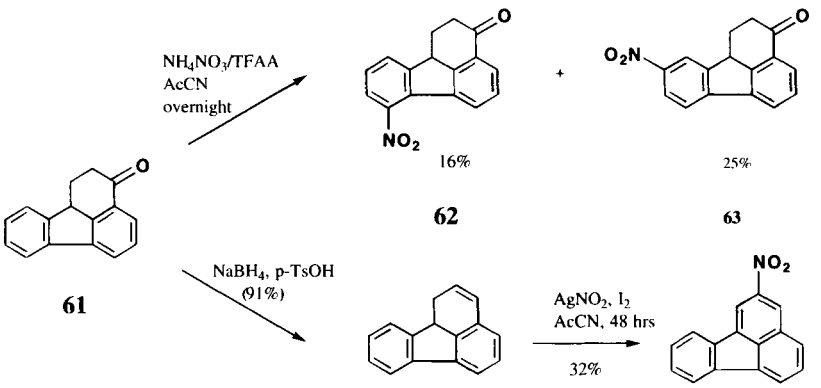
Structures and Numbering System of fluoranthene and its polycyclic derivatives. The numbers in parentheses indicate the positions of nitro substitution for which compounds have been synthesized and characterized.



(16)

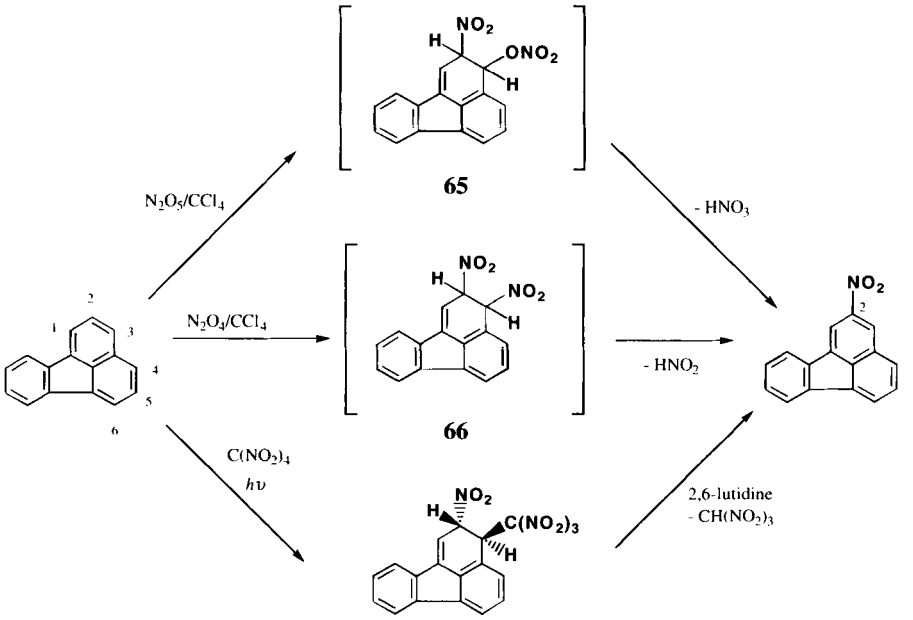
60

CHO



Scheme 3

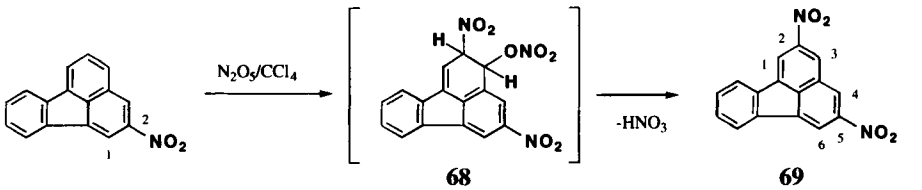
Zielinska *et al*[27] obtained 2-nitrofluoranthene in 30% yield as the sole mononitro isomer upon the treatment of fluoranthene with an equimolar amount of N_2O_5 in CCl_4 at 25° (Scheme 4).



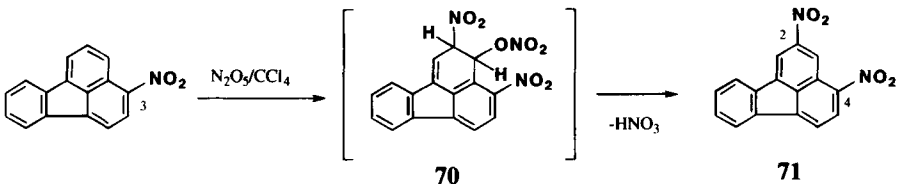
Scheme 4

This represents the first preparative direct one step synthesis of 2-nitrofluoranthene, which was previously available only through a lengthy directed nitration procedure.[88] This, coupled with recent identification of 2-nitrofluoranthene in ambient air samples[3,4,15] has prompted intense investigation of the

nitration of polyarenes with lower nitrogen oxides such as N_2O_5 or N_2O_4. Squadrito *et al* [89,90] have found that the positional selectivity in the N_2O_4 nitration of fluoranthene is highly dependent on the nature of the solvent: *i.e.*, the relative distribution (~54%) of 2-nitrofluoranthene obtained in CCl_4 was much greater than in CH_2Cl_2 (~2%). This suggests that the operating mechanism in the low dielectric solvent CCl_4 is exclusively a homolytic radical nitration, involving an addition-elimination reaction. Eberson *et al*[91] isolated a novel adduct **67** in 25% yield from a photolysis mixture of the charge-transfer complex of fluoranthene and tetranitromethane in CH_2Cl_2 and showed that it could be converted cleanly into 2-nitrofluoranthene in the presence of 2,6-lutidine, presumably by an elimination of nitroform (Scheme 4). The latter reaction is of interest since similar adducts **65** and **66** have been postulated as possible intermediates for the formation of 2-nitrofluoranthene *via* elimination of HNO_3[27] and HNO_2,[89,90] respectively (Scheme 4). Zielinska *et al*[92] have recently isolated and presented convincing spectroscopic evidence of the intermediate adducts **68** and **70** that can lead to 2,5- and 2,4-dinitrofluoranthene (**69** and **71**), respectively, through a radical multistep addition-elimination mechanism (Eqs. 17 and 18). The adducts **68** and **70** were produced by nitration of 2- and 3-nitrofluoranthene, respectively with N_2O_5 in CCl_4.



68 **69** (17)



70 **71** (18)

6. Polycyclic Fluoranthenes

Despite the widespread environmental presence of polycyclic fluoranthenes, very little is known concerning their chemistry.[57,93] Cho *et al*[94] have described the first systematic investigation of nitration reactions of several polycyclic fluoranthenes: benz[e]acephenanthrylene, benz[a]aceanthrylene, indeno[1,2,3-cd]pyrene, indeno[1,2,3-hi]chrysene, dibenz[a,e]aceanthrylene, dibenz[a,j]aceanthrylene and dibenz[e,k]acephenanthrylene (Fig. 3). The direct N_2O_4 nitration of these fluoranthenes in CH_2Cl_2 proceeded with remarkable regioselectivity at the 8-, 8-, 12-, 5-, 14-, 5- and 9-positions, respectively, to provide single mononitro products. In the case of benz[e]acephenanthrylene, 17% of the 1-nitro isomer was isolated. 12-Nitroindeno[1,2,3-cd]pyrene was also the

CHO

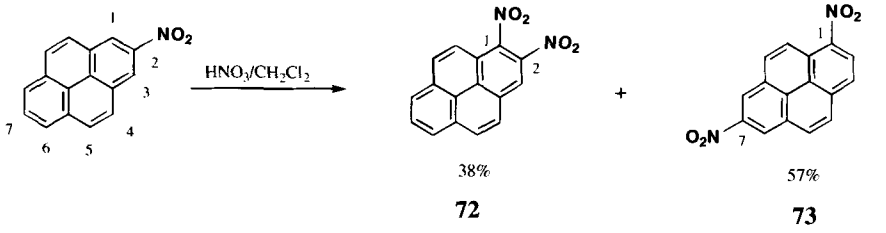
major product with acetyl nitrate and found to be 77 times more mutagenic than the parent hydrocarbon in TA98 in the presence of S9 mix.[95] The structures of all eight mononitro isomers were fully characterized by analysis of their COSY and NOESY spectra and by comparison with the spectra of the parent hydrocarbons.[94,96]

As with other electrophilic substitution patterns (*e.g.*, acylation and bromination),[97] the observed nitration sites of the polycyclic fluoranthenes were in excellent agreement with theoretical predictions made by the DEWAR-PI method,[22] which has been devised specifically for non-alternant polyarenes. Although nitration with both N_2O_4 and HNO_3 under controlled conditions gave similar reaction profiles on HPLC, the nitration with N_2O_4 was more rapid and afforded cleaner products.[94]

III. DINITROPOLYARENES

Dinitropolyarenes have been found to be considerably more mutagenic and tumorigenic than mononitropolyarenes. Unlike mononitropolyarenes, the number of possible dinitro isomers for a given polyarene increases exponentially. For example, while there exist 25 dinitrofluoranthenes, only 5 mononitro isomers are possible.[98] In general, dinitropolyarenes are synthesized either by direct dinitration of the parent polyarene or by a further nitration of mononitropolyarenes.

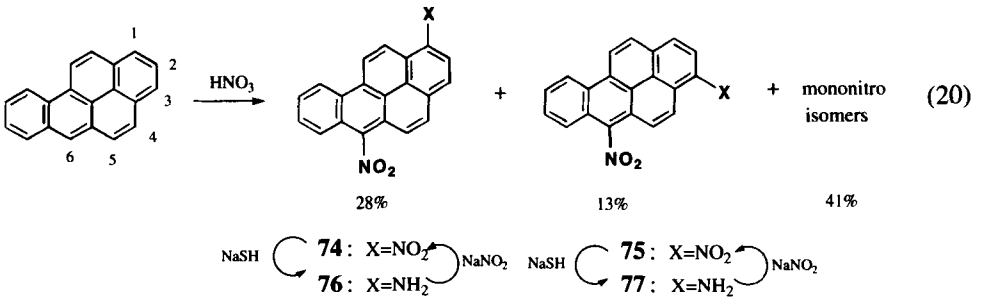
Direct dinitration of pyrene or a further nitration of 1-nitropyrene with excess HNO_3 furnished three dinitropyrenes (1,3-, 1,6- and 1,8-), with the 1,8-isomer being predominant.[5] Two rare dinitropyrenes **72** (1,2-isomer) and **73** (1,7-isomer) have been synthesized in 38 and 57% yield, respectively, by a further nitration of 2-nitropyrene (Eq. 19).[99] The relative ease of ortho substitution



72 **73** (19)

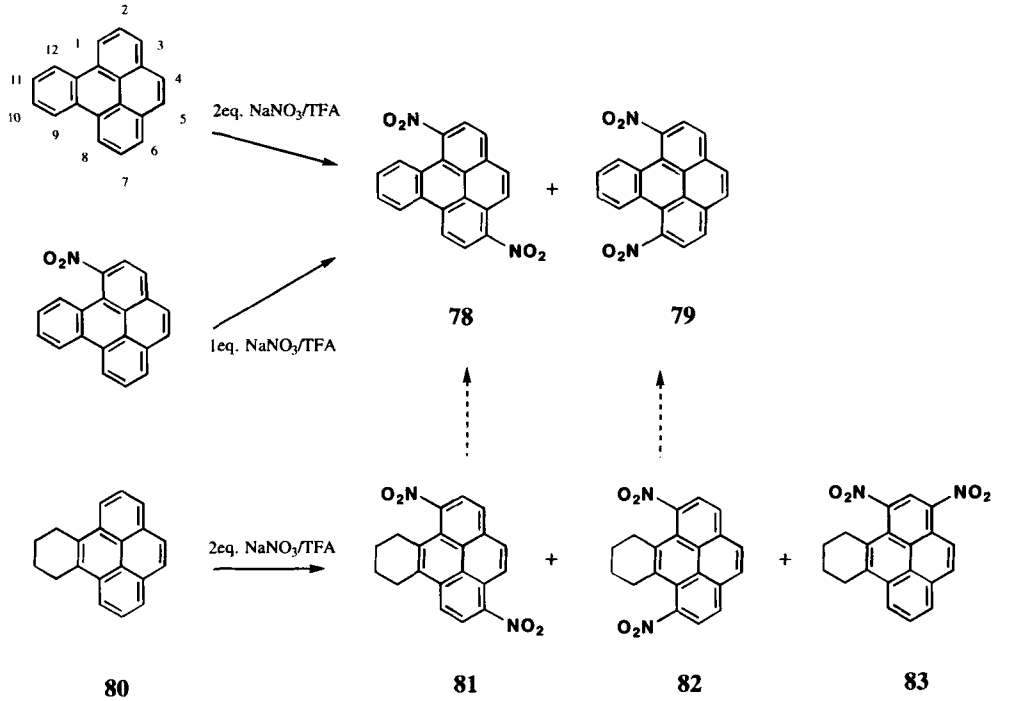
observed in **72** is presumably due to a weak interaction of the nitro group and the aromatic moiety, as indicated by UV, NMR and mass spectral data.[46] An alternate synthesis of **72**, involving a multi-step sequence has also been reported.[100]

Direct dinitration of BaP using a large excess of HNO_3 resulted in 1,6- (**74**) and 3,6-dinitro-BaP (**75**) (28 and 13%, respectively), along with a mixture of mononitro-BaP derivatives (41%)(Eq. 20).[63] Due to the difficulty of separation, **74** and **75** were partially reduced with NaSH to aminonitro-BaP derivatives (**76** and **77**), which after separation on silica, were converted back to **74** and **75**, respectively, *via* a diazonium salt procedure ($NaNO_2/H_2SO_4$) (Eq. 20).[63]



(20)

Both the direct dinitration of BeP or a further nitration of 1-nitro-BeP with $NaNO_3$/TFA in acetic anhydride yielded 1,6- and 1,8-dinitro-BeP (*e.g.*, **78** and **79**)(Scheme 5).[69] Curiously, a further nitration of 3-nitro-BeP gave **78** as the sole dinitro product. The absence of 3,6-dinitro-BeP in the above reactions is contrasted with the fact that bromination of BeP with excess bromine yields exclusively 3,6-dibromo-BeP. On the other hand, direct dinitration of the tetrahydro-BeP **80**



Scheme 5

furnished three (1,3-, 1,6- and 1,8-) dinitro analogs (*e.g.*, **81**, **82** and **83**), which could be dehydrogenated to afford the desired dinitro-BePs. This result is consistent with the fact that **80** contains a pyrene moiety and that both dinitration and a further nitration of pyrene afford three dinitro isomers (1,3-, 1,6- and 1,8-pyrene). The lack of the 3,6-dinitro isomer suggested that steric effects play a minimal role in the nitration of BeP and its tetrahydro analog **80**.[69]

CHO

Direct dinitration of perylene (Fig. 1) with a large excess (20 eq.) of HNO_3 produced at least four dinitro derivatives (3,6-, 3,7-, 3,9-, 3,10-) in a 5:1:1:2 ratio in 60% overall yield.[73] The four dinitro isomers were partially separated and analyzed by ^1H NMR. The mixture of the 3,9- and 3,10-dinitro isomers was found to be about 100 times more mutagenic than 3-nitroperylene in the Ames test using *Salmonella Typhimurium* TA98.

Using a combination of direct and further nitration approaches, Ramdahl *et al*[98] have prepared 18 out of 25 possible dinitrofluoranthenes (Fig. 3) and examined their EI mass and ^1H NMR spectral patterns. Nitration with N_2O_5 in CCl_4 provided rare isomers, such as 1,2-, 1,3-, 2,3-, 2,4- and 2,5-dinitrofluoranthenes, which are not typically formed by traditional electrophilic nitrations.[83,92,98]

IV. OXYGENATED NITROPOLYARENES

Nitropolyarenes are metabolized either by nitroreduction or ring oxidation pathways, or a combination of both. Oxygenated nitropolyarenes are an important class of substituted nitropolyarenes, which arise from the ring oxidation pathway and include the phenolic, quinnoid and dihydrodiol epoxide derivatives.[14] Metabolism studies have shown that, as in the case of polyarenes, the dihydrodiol and diol epoxide derivatives are major proximate and ultimate mutagenic metabolites of nitropolyarenes.[14] The availability of these nitropolyarene derivatives, therefore, will permit the systematic metabolism studies of DNA adduct formation and tumorigenicity. The environmental occurrence of the phenolic and quinnoid nitropolyarenes *via* photochemical reactions has been documented and some of these derivatives were found to be mutagenic.[46,55,101]

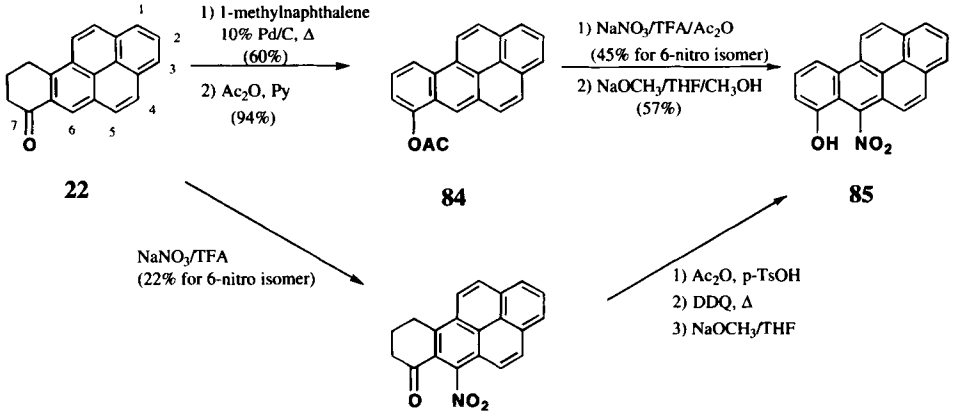
1. Phenolic Nitropolyarenes

Phenolic nitropolyarenes are synthesized by several different routes: (i) nitration of acetoxylated-polyarenes or acetoxylation of nitro-ketoarenes, followed by methanolysis; (ii) osmylation and acetylation of nitropolyarenes, followed by base-catalyzed elimination and hydrolysis; (iii) direct acetoxylation of nitropoly-arenes, followed by base hydrolysis and (iv) photolysis of nitropolyarenes.

A typical example of the first (i) procedure is the preparation of 7-hydroxy-6-nitro-BaP (**85**), which consisted of acetoxylation of the commercially available 8-keto-BaP **22**, followed by nitration and methanolysis (Scheme 6).[70] Alternatively, **85** was prepared by initial nitration of **22**, followed by acetoxylation. The latter was the sequence of choice for the preparation of the nitro derivatives (1-, 2-, ad 3-nitro) of 9-hydroxy-BaP, which were found difficult to separate in the final stage. The ease of separating positional isomers formed in a given nitration step is a determining factor for choosing the reaction sequence. Several phenolic derivatives of nitro-BaP and nitro-BeP have been prepared by these methods.[70,102]

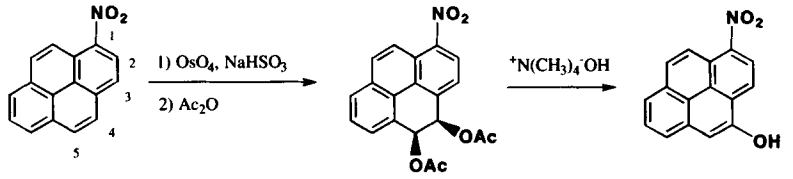
The second (ii) approach is particularly suited for introducing a hydroxy group at the K-region of polyarenes.[11,102] Osmylation of 1-nitropyrene in the presence of acetic anhydride gave the *cis*-dihydrodiol acetate **87**, which after base-catalyzed elimination and hydrolysis afforded 4-hydroxy-1-nitropyrene (**88**)(Eq. 21).[11] A typical example of the third (iii) procedure is the direct acetoxylation of 2-nitropyrene with $Pb(OAc)_4$, which after hydrolysis gave a 1:1.7 mixture of **89** and **90** in 35%

yield (Eq. 22).[99] The relative ease of separating the two isomers (**89** and **90**) on silica is probably due to the low polarity of **89**, which has a unique intramolecular hydrogen bonding capability. The synthesis of **89** was also possible either by nitration of 1-hydroxypyrene (4%) or by photolysis of 1-nitropyrene (7%, *via* rearrangement), but their low yields make them of less practical synthetic utility.[46] Nonetheless, photolysis is a useful technique for preparing certain rare phenolic nitropolyarenes that are otherwise difficult to obtain.[101]



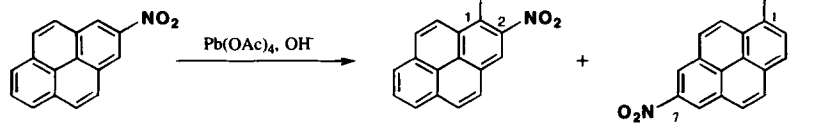
22 **84** **85** **86**

Scheme 6



(21)

87 **88**



(22)

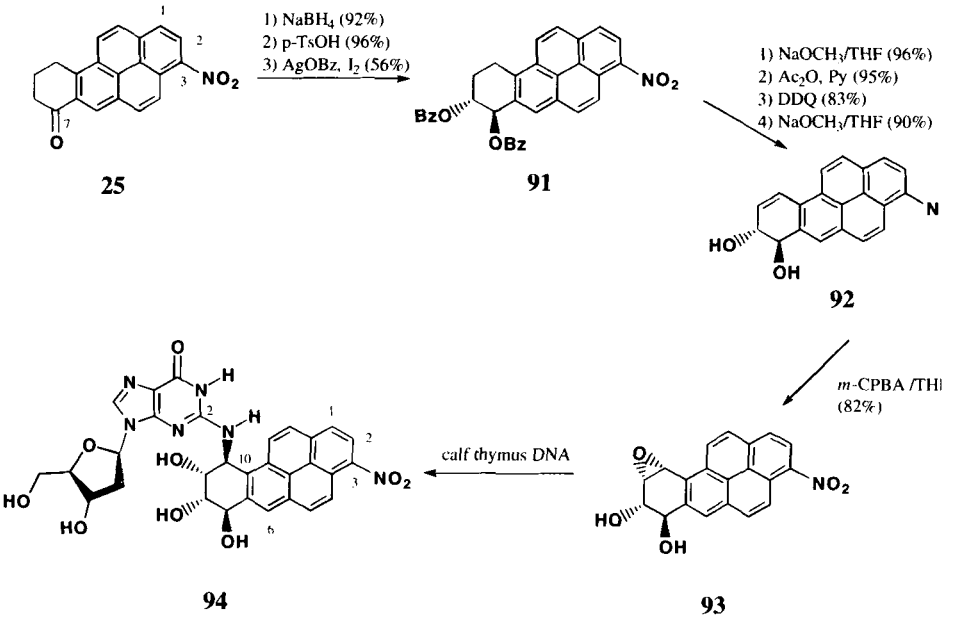
89 **90**

2. Diolepoxides of Nitropolyarenes

Fu *et al*[66,67] have recently reported the synthesis of 1- and 3-nitro-BaP *trans*-7,8-diol *anti*-9,10-epoxide, which represented the first total synthetic preparation of nitropolyarenes containing a bay region diol epoxide moiety. Scheme 7 outlines the preparation of the *trans* diol epoxide of 3-nitro-BaP (**93**) as an example.[66] Conversion of **25** to the final diol epoxide **93** was carried out in 28 %

CHO

overall yield by following the well-known sequence for the synthesis of BaP *trans*-7,8-diolepoxide.[57] The 1-nitro analog of **93** was similarly prepared in 28 % yield starting from 1-nitro-7-keto-BaP (**24**).[67] The usual dehydrogenation attempt of **91** with DDQ in refluxing benzene or dioxane was unsuccessful, presumably due to the steric hindrance caused by bulky benzoate groups and the electron withdrawing effect of the nitro group on hydride abstraction by DDQ. As a result, **91** was hydrolyzed, acetylated and dehydrogenated with DDQ in refluxing dioxane to afford **92** in 68% yield. Analogous to the diol epoxides derived from a majority of polyarenes,[57] the *in vitro* reaction of **93** with calf thymus DNA resulted in the formation of N^2-substituted 2'-deoxyguanosine (**94**) as the major DNA adduct (Scheme 7).[66]



Scheme 7

V. SUMMARY

The synthetic availability and purity of nitropolyarenes play a crucial role in their subsequent identification from complex environmental pollutant mixtures and in the study of their structure-activity relationships. Although direct nitration of the parent polyarene provides a simple and convenient access of nitropolyarenes, it is limited to the preparation of those substituted at reactive positions. Direct nitration frequently results in a mixture of mono- and di-nitro isomers, that requires rigorous separation efforts. Svendsen *et al*[24] pointed out the importance of isomeric purity when dealing with the nitrotripenylene isomers. Since 2-nitrotriphenylene (Fig. 1) is about 10,000 times more mutagenic than the 1-nitro isomer, even a minute (*e.g.*, <0.1%) contamination of the 2-nitro isomer in the assay of the 1-isomer will furnish a false biological result. Consequently, considerable efforts have been directed towards the development of efficient and regiospecific preparation of

nitropolyarenes. Among the many available indirect nitration approaches, nitration of partially hydrogenated polyarenes followed by aromatization, continues to be the most popular route. The basic strategy is that partial saturation of a polyarene creates a new aromatic system, whose substitution pattern is totally different from the parent hydrocarbon (*e.g.*, 2-nitropyrene in Scheme 1 and 2-nitro-BaP in Eq. 5).[31] The new synthesis of 2-nitrofluoranthene by van Haeringen *et al*[86] comprises an intriguing example of a regiospecific synthesis, which consisted of a selective nitration ($AgNO_2/I_2$ in acetonitrile) at the β-position of a conjugated double bond of a partially hydrogenated fluoranthene (*e. g.*, **64** in Scheme 3). The use of a hydrogenated polyarene containing a keto group as the starting material is another popular indirect nitration approach, in which the deactivating effect of the keto function causes nitration to occur at the distant aromatic rings (*e.g.*, 8-nitro-4*H*-cyclopenta[def]phenanthrene in Eq. 15).[82] The direct oxidation of aminoarenes is also an attractive option, since a number of aminoarenes are commercially (aminoanthracenes) and/or synthetically (amino-phenanthrenes,[30] amino-BcPs,[60] and amino-BaPs,[68] *etc.*) available.

Nitration with nitrogen oxides such as N_2O_4 and N_2O_5 has been of considerable interest due to their high reactivity towards polyarenes[33,37,89,90,92] and environmental relevance.[15,27] Dimeric N_2O_4 exists in equilibrium with monomeric NO_2, with the former being predominant in solution. Nitration with N_2O_4 (1) is fast, (2) produces high yields of clean nitrated products at room-temperature, (3) exhibits a high degree of regioselectivity and (4) requires easy work-up procedures. Thus, N_2O_4 is regarded as the best nitrating reagent for small scale preparation of nitropolyarenes. However, care should be exercised in selecting experimental conditions, such as the drying and choice of solvents, temperature and catalysts, *etc.*, as they have a direct impact on the relative isomer distribution *via* different mechanisms (*e.g.*, ionic *vs* radical).[90]

Finally, preparation of reactive diol epoxide derivatives of nitropolyarenes is expected to be an important and challenging area in future nitropolyarene syntheses, since their availability is crucial for the study of biological activities, including DNA adduct formation and tumorigenicity.[66,67]

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REFERENCES

1. *IARC Monograph on the Evaluation of the Carcinogenic Risks of Chemicals to Humans: Diesel and Gasoline Engine Exhausts and Some Nitroarenes*; IARC: Lyon, France; **Vol. 46** (1989).

2. H. S. Rosenkranz and R. Mermelstein, *Mutat. Res.*, **114**, 217 (1983).

3. T. Ramdahl, B. Zielinska, J. Arey, R. Atkinson, A. M. Winer and J. N. Pitts Jr., *Nature*, **321**, 425 (1986).

4. J. N. Pitts Jr., *Atmos. Environ.*, **21**, 2531 (1987).

5. M. C. Paputa-Peck, R. S. Marano, D. Schuetzle, T. L. Riley, V. C. Hampton, T. J. Prater, L. M. Skewes, T. E. Jensen, P. H. Ruehle, L. C. Bosch and W. P. Duncan, *Anal. Chem.*, **55**, 1946 (1983).

6. A. Robbat Jr., N. P. Corso, P. J. Doherty and M. H. Wolf, *ibid.*, **58**, 2078 (1986).

7. J. M. Bayona, K. E. Markides and M. L. Lee, *Environ. Sci. Technol.*, **22**, 1440 (1988).

8. H. Tokiwa and Y. Ohnishi, *CRC Crit. Rev. Tox.*, **17**, 23 (1986).

9. K. El-Bayoumy, *Chem. Res. Tox.*, **5**, 585 (1992).

10. S. S. Hecht and K. El-Bayoumy, "*Nitroarenes: Occurrence, Metabolism and Biological Impact,*" Edited by P. C. Howard, S. S. Hecht and F. A. Beland, p. 309, Plenum, New York, NY, 1990.

11. P. H. Ruehle, L. C. Bosch and W. P. Duncan, "*Nitrated Polycyclic Aromatic Hydrcarbons;*" Edited by C. M. White, p.169, Hüthig, Heidelberg, 1985.

12. M. J. S. Dewar, *Rec. Chem. Progress*, **19**, 1 (1958).

13. J. N. Pitts Jr., K. A. Van Cauwenberghe, D. Grosjean, J. P. Schmid, D. R. Fitz, W. L. Belser, G. B. Knudson and P. M. Hynds, *Science*, **202**, 515 (1978).

14. P. P. Fu, *Drug Metab. Rev.*, **22**, 209 (1990).

15. B. Zielinska, J. Arey and R. Atkinson, "*Nitroarenes: Occurrence, Metabolism and Biological Impact,*" Edited by P. C. Howard, S. S. Hecht and F. A. Beland, p. 73, Plenum, New York, NY, 1990.

16. A. K. Debnath, R. L. L. de Compadre, G. Debnath, A. J. Shusterman and C. Hansch, *J. Med. Chem.*, **34**, 786 (1991).

17. T. Nielsen, *Environ. Sci. Technol.*, **18**, 157 (1984).

18. J. Arey, B. Zielinska, R. Atkinson and S. M. Aschmann, *Int. J. Chem. Kinetics*, **21**, 775 (1989).

19. T. Greibrokk, B. Iversen, E. J. Johansen, H.-P. Renningsen and H. Svendsen, *J. High Res. Chrom. & Chrom. Commun.*, **1**, 671 (1984).

20. K. Fukuhara, A. Hakura, N. Sera, H. Tokiwa and N. Miyata, *Chem. Res. Tox.*, **5**, 149 (1992).

21. M. J. S. Dewar and E. W. T. Warford, *J. Chem. Soc.*, 3570 (1956).

22. M. J. S. Dewar and R. D. Dennington II, *J. Am. Chem. Soc.*, **111**, 3804 (1989).

23. T. Yoshikawa, W. Flory, L. P. Ruhr, D. Giamalva, D. F. Church and W. A. Pryor, *Vet. Hum. Tox.*, **29**, 25 (1987).

24. H. Svendsen, H.-P. Rønningsen, L. K. Sydnes and T. Greibrokk, *Acta Chem. Scand.*, **B37**, 833 (1983).

25. H. Heaney, A. J. Jones and I. T. Millar, *J. Chem. Soc.*, 2587 (1965).

26. M. C. Judd, M. P. Hartshorn, R. J. Martyn, W. T. Robinson, G. J. Wright and R. W. Vannoort, *Australian J. Chem.*, **43**, 125 (1990).

27. B. Zielinska, J. Arey, R. Atkinson, T. Ramdahl, A. M. Winer and J. N. Pitts Jr, *J. Am. Chem. Soc.*, **108**, 4126 (1986).

28. D. H. Hey and J. M. Osbond, *J. Chem. Soc.*, 3172 (1949).

29. P. M. G. Bavin and M. J. S. Dewar, *ibid.*, 4477 (1955).

30. M. L. Tedjamulia, Y. Tominaga, M. Sugiura, H. Kudo, M. L. Lee and R. N. Castle, *Polynucl. Aromat. Hydrocarbons, Int. Symp., 7th 1982*, p. 1161, 1983.

31. D. W. Miller, D. Herreno-Saenz, K. H. Huang, T. M. Heinze and P. P. Fu, *J. Org. Chem.*, **57**, 3746 (1992).

32. I. C. Calder and P. J. Williams, *Australian J. Chem.*, **27**, 1791 (1974).

33. F. Radner, *Acta Chem. Scand.*, **B37**, 65 (1983); L. Eberson and F. Radner, *ibid.*, **B39**, 343 (1985).

34. H. M. Chawla and R. S. Mittal, *Synthesis*, 70 (1985).

35. C. E. Braun, C. D. Cook, C. Merritt Jr. and J. E. Rousseau, *Org. Synth.*, **Coll. Vol. 4**, 711, 1963.

36. G. A. Olah, R. Malhorta and S. C. Narang "*Nitration Methods and Mechanisms*;" VCH, New York, NY, 1989.

37. W. A. Pryor, G. J. Gleicher, J. P. Cosgrove and D. F. Church, *J. Org. Chem.*, **49**, 5189 (1984).

38. G. L. Squadrito, F. R. Fronczek, S. F. Watkins, D. F. Church and W. A. Pryor, *ibid.*, **55**, 4322 (1990).

39. J. E. Baldwin, A. G. Swanson, J. K. Cha and J. A. Murphy, *Tetrahedron*, **42**, 3943 (1986).

40. J. D. Scribner and J. A. Miller, *J. Chem. Soc.*, 5377 (1965).

41. J. P. Alazard, H. B. Kagan and R. Setton, *Bull. Soc. Chim. Fr.*, 499 (1977).

42. T. Kato, N. Tadokoro, M. Tsutsui and K. Kikugawa, *Mutat. Res.*, **249**, 243 (1991).

43. H. Sharghi and F. Tamaddon, *Syn. Commun.*, **21**, 2349 (1991).

44. M. Konieczny and R. G. Harvey, *Org. Synth.*, **62**, 165 (1984).

45. K. Imaida, M. Hirose, L. Tay, M.-S. Lee, C. Y. Wang and C. M. King, *Cancer Res.*, **51**, 2902 (1991).

46. A. M. van den Braken-van Leersum, C. Tintel, M. van't Zelfde, J. Cornelisse and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas,* **106**, 120 (1987).

47. A. J. Fatiadi and L. R. Hilpert, *J. Labelled Compd. Radiopharm.*, **27**, 129 (1989).

48. R. Bolton, *J. Chem. Soc.*, 4637 (1964).

49. P. P. Fu, H. M. Lee and R. G. Harvey, *J. Org. Chem.*, **45**, 2797 (1980).

50. P. M. G. Bavin, *Can. J. Chem.*, **37**, 1614 (1959).

51. M. J. S. Dewar, T. Mole, D. S. Urch and E. W. T. Warford, *J. Chem. Soc.*, 3572 (1956).

52. K. El-Bayoumy, D. Desai, P. Upadhyaya, S. Amin and S. S. Hecht, *Carcinogenesis*, **12**, 2271 (1992).

53. M. S. Newman and K. C. Lilje, *J. Org. Chem.*, **44**, 1347 (1979).

54. B. Iversen, L. K. Sydnes and T. Greibrokk, *Acta Chem. Scand.*, **B39**, 837 (1985).

55. H. Johansen, J. Doehl and T. Greibrokk, *J. Chrom. Sci.*, **27**, 378 (1989).

56. P. M. G. Bavin and M. J. S. Dewar, *J. Chem. Soc.*, 164 (1956).

57. R. G. Harvey, *Polycyclic Aromatic Hydrocarbons, Chemistry and Carcinogenicity*, Cambridge University Press, Cambridge, 1991.

58. L. H. Klemm, E. Hall and S. K. Sur, *J. Heterocycl. Chem.*, **25**, 1427 (1988).

59. M. S. Newman and A. I. Kosak, *J. Org. Chem.*, **14**, 375 (1949).

60. M. S. Newman and J. Blum, *J. Am. Chem. Soc.*, **84**, 1835 (1964)

61. H. Glatt, A. Piée, K. Pauly, T. Steinbrecher, R. Schrode, F. Oesch and A. Seidel, *Cancer Res.*, **51**, 1659 (1991).

62. E. Johansen, L. K. Sydnes and T. Greibrokk, *Acta Chem. Scand.*, **B38**, 309 (1984).

63. K. Fukuhara, N. Miyata, M. Matsui, K. Matsui, M. Ishidate Jr. and S. Kamiya, *Chem. Pharm. Bull. Jpn.*, **38**, 3158 (1990).

64. J. M. Pitts Jr., B. Zielinska and W. P. Harger, *Mutat. Res.*, **140**, 81 (1984).

65. M. W. Chou, R. H. Heflich, D. A. Casciano, D. W. Miller, J. P. Freeman, F. E. Evans and P. P. Fu, *J. Med. Chem.*, **27**, 1156 (1984).

66. P. P. Fu, Y.-S. Wu, L. S. Von Tungeln, J.-S. Lai, M. P. Chiarelli and F. E. Evans, *Chem. Res. Tox.*, **6**, 603 (1993).

67. Y.-S. Wu, J.-S. Lai and P. P. Fu, *J. Org. Chem.*, **58**, 7283 (1993).

68. P. P. Fu, R. H. Heflich, D. A. Casciano, A. Y. Huang, W. M. Trie, F. F. Kadlubar and F. A. Beland, *Mutat. Res.*, **94**, 13 (1982).

69. Y. S. Wu, Y. K. Wang, C. C. Lai, J. S. Lai, L. E. Unruh, F. E. Evans and P. P. Fu, *Polynucl. Aromat. Hydrocarbons, Meas., Means, Metab., Int. Symp., 11th 1987*, p. 1083, 1991.

70. M.-J. Lee, E. Cheng and P. P. Fu, *Org. Prep. Proced. Int.*, Submitted (1995).

71. C. V. Ristagno and H. J. Shine, *J. Am. Chem. Soc.*, **93**, 1811 (1971).

72. L. Eberson and F. Radner, *Acta Chem. Scand.*, **B39**, 357 (1985).

73. A. Nordbotten, L. K. Sydnes and T. Greibrokk, *Acta Chem. Scand.*, **B38**, 701 (1984).

74. J. J. Looker, *J. Org. Chem.*, **37**, 3379 (1972).

75. H. Jung, A. U. Shaikh, R. H. Heflich and P. P. Fu, *Environ. Mol. Mutagen.*, **17**, 169 (1991).

76. P. P. J. Mulder, J. O. Boerrigter, B. B. Boere, H. Zuilhof, C. Erkelens, J. Cornelisse and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **112**, 287 (1993).

77. W.-W. Sy and A. W. By, *Tetrahedron Lett.*, **26**, 1193 (1985).

78. A. M. van den Braken-van Leersum, N. M. Spijker, J. Lugtenburg and J. Cornelisse, *Recl. Trav. Chim. Pays-Bas*, **106**, 628 (1987).

79. A. M. van den Braken-van Leersum, J. Cornelisse and J. Lugtenburg, *Tetrahedron Lett.*, **26**, 4823 (1985).

80. J. M. Goldring, L. M. Ball, R. Sangaiah and A. Gold, *Mutat. Res.* **187**, 67 (1987).

81. M. Minabe, R. Nishimura, T. Kimura and M. Tsubota, *Bull. Chem. Soc. Jpn.*, **66**, 1248 (1993).

82. M. Yoshida, S. Nagayama, M. Minabe and K. Suzuki, *J. Org. Chem.*, **44**, 1915 (1979).

83. B. Zielinska, J. Arey, W. P. Harger and R. W. K. Lee, *Mutat. Res.*, **206**, 131 (1988).

84. G. L. Squadrito, B. S. Shane, F. R. Fronczek, D. F. Church and W. A. Pryor, *Chem. Res. Tox.*, **3**, 231 (1990).

85. A. Streitwieser Jr. and R. C. Fahey, *J. Org. Chem.*, **27**, 2352 (1962).

86. C. J. van Haeringen, N. F. Aten, J. Cornelisse and J. Lugtenburg, *Recl. Trav. Chim. Pays-Bas*, **111**, 335 (1992);

87. M. J. S. Dewar and J. Michl, *Tetrahedron*, **26**, 375 (1970).

88. M. C. Kloetzel, W. King and J. H. Menkes, *J. Am. Chem. Soc.*, **78**, 1165 (1956).

89. G. L. Squadrito, D. F. Church and W. A. Pryor, *ibid.*, **109**, 6535 (1987).

90. G. L. Squadrito, F. R. Fronczek, D. F. Church and W. A. Pryor, *J. Org. Chem.*, **55**, 2616 (1990).

91. L. Eberson, M. P. Hartshorn, F. Radner and W. T. Robinson, *Acta Chem. Scand.*, **47**, 410 (1993).

92. B. Zielinska, J. Arey and W P. Harger, *Polynucl. Aromat. Hydrocarbons, Meas., Means, Metab., Int. Symp., 11th, 1987*, p. 1107, 1991.

93. B. P. Cho and R. G. Harvey, *J. Org. Chem.*, **52**, 5668 (1987).

94. B. P. Cho, M. Kim and R. G. Harvey, *ibid.*, **58**, 5788 (1993).

95. M. Minabe and N. Shibuya, *Chem. Res. Tox.*, **2**, 357 (1989).

96. B. P. Cho and R. G. Harvey, *J. Org. Chem.*, **52**, 5679 (1987).

97. M. Minabe, B. P. Cho and R. G. Harvey, *J. Am. Chem. Soc.*, **111**, 3809 (1989).

98. T. Ramdahl, B. Zielinska, J. Arey and R. W. Kondrat, *Biomed. Environ. Mass Spectrum*, **17**, 55 (1988).

99. A. M. van den Braken-van Leersum, J. Cornelisse and J. Lugtenburg, *Chem. Commun.*, 1156 (1987).

100. M. Minabe, H. Mochizuki, M. Yoshida and T. Toda, *Bull. Chem. Soc. Jpn.*, **62**, 68 (1989).

101. M. P. Holloway, M. C. Biaglow, E. C. McCoy, M. Anders, H. S. Rosenkranz and P. C. Howard, *Mutat. Res.*, **187**, 199 (1987).

102. Y. C. Wu, C. C. Lai, P. P. Fu and L. E. Unruh, *J. Chin. Chem. Soc. (Taipei)*, **35**, 159 (1988), *Chem. Abstr.*, **110**: 114433p (1989)

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