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ATTEMPTS TO PREPARE AROMATIC O-ACYL-HYDROXYLAMINES—I

DEHYDROHALOGENATION OF 1-BROMO-4-ACETOXYIMINO-1,2,3,4-TETRAHYDROPHENANTHRENE BY TETRAMETHYLAMMONIUM DIMETHYLPHOSPHATE

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Abstract—The dehydrohalogenation of 1-bromo-4-acetoxyimino-1,2,3,4-tetrahydrophenanthrene by tetramethylammonium dimethylphosphate gave a mixture of products. Ten of these were identified and together account for 70% of the total yield. The proposed reaction mechanism implicates the corresponding O-acetyl-hydroxylamine **15** as an intermediate. Attempts to prepare O-esters or O-ethers of aromatic hydroxylamines by dehydrogenation, with quinones, of the corresponding oximino-derivatives of oxo-1,2,3,4-tetrahydro-naphthalene and oxo-1,2,3,4-tetrahydro-phenanthrene were without success.

It is currently believed that carcinogenic aromatic amines and amides are metabolised in mammalian tissues, via their proximate carcinogenic N-hydroxy-derivatives,[1,2] to certain electrophilic forms (ultimate carcinogens).[3] These may be directly responsible for the initiation of carcinogenesis by reacting with nucleophilic residues in critical cellular components (for instance nucleic acids and proteins). The rat liver carcinoma induced by administration of N-hydroxy-2-acetylaminofluorene (N-hydroxy-AAF) to male rats is probably mediated at least in part by the sulphate ester as ultimate carcinogen.[3]

After feeding rats on N-hydroxy-AAF, DNA isolated from the liver yielded, on enzymatic hydrolysis, two amino-fluorene-derivatised deoxyguanine residues. These were identified as deoxyguanine-aminofluorene (dG-AF) and deoxyguanine-acetyl-aminofluorene (dG-AAF) and occured in the molar ratio 2:1 respectively.[4-6] However, *in vitro* reaction of the sulphate ester of N-hydroxy-AAF with DNA under physiological conditions gave dG-AAF only.[7] This suggests that, for the AF-bound residue at least, other activated electrophilic species may also be involved. A number of possible routes leading to the formation of the AF-bound residue have been proposed.[8-12] Of particular interest is the recent report[13] that strong electrophilic O - acetyl - derivatives of N-hydroxyamino arenes may account for the way in which the amino function of the carcinogen is able to bind residues in nucleic acids and proteins (Scheme 1). These O-acetyl derivatives of N-hydroxyaminoarenes are formed by enzymatic transacetylation from N - hydroxy - N - acetylamino - arenes to N - hydroxyamino - arenes by liver cytosol. The transacetylase activity, however, is not tissue specific since it has also been shown to occur in kidney, small intestinal mucosa and mammary tissue.[14] Electrophilic O-acetyl derivatives of aromatic hydroxylamines, therefore, would appear to be candidates as ultimate carcinogens in target tissues. (They would also explain the formation of dG-AF mentioned above). This consideration prompted us to attempt the synthesis of aromatic O-acyl-hydroxylamines and to study their properties, since to the best of our knowledge no systematic study of this nature has been reported.

During this investigation 4-substituted phenanthrene was selected as a model compound for two reasons. Firstly the O-acyl derivatives obtained from either sterically hindered hydroxylamines (or sterically hindered acylating agents) have been described as being relatively more stable than unhindered analogs.[15,16] Secondly, the 2-substituted acetaminophenanthrene isomer, its N-hydroxy, N-acyl-N-hydroxy and N-acyl-N-acetoxy derivatives are all potential carcinogens.[2,17]

O - Acyl - derivatives of hydroxylamines have been prepared by Carpino's method.[18] Although Millers *et al.*[14] failed to synthesise aromatic O-acylhydroxylamines from parent hydroxylamines, synthesis of N - (2,4 - dinitrophenyl) - O - acetyl - hydroxylamine and the analogous O-benzoyl derivative has been achieved from its corresponding hydroxylamine.[19] This is probably due to the stabilizing effect afforded by the presence of the electronwithdrawing nitro-groups.

During our attempts to prepare O-derivatives of aromatic hydroxylamines we have explored two possible methods (i) dehydrobromination of 1 - brom - 4 - acetoximino - 1,2,3,4 - tetrahydrophenanthrene **4** and (ii) dehydrogenation of oxyimino derivatives of oxo - 1,2,3,4 - tetrahydro - napthalene and oxo - 1,2,3,4 - tetrahydrophenanthrene with quinones.

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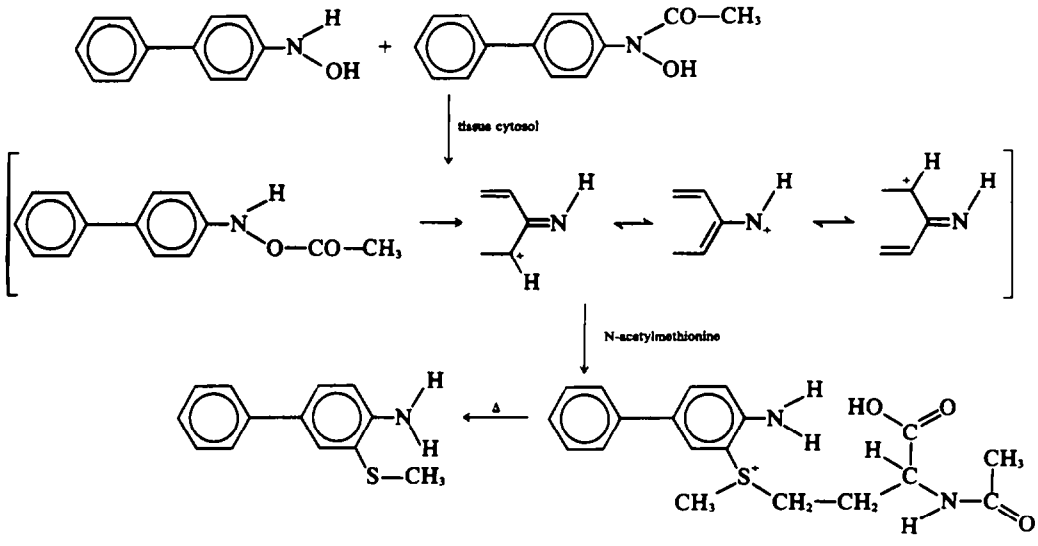
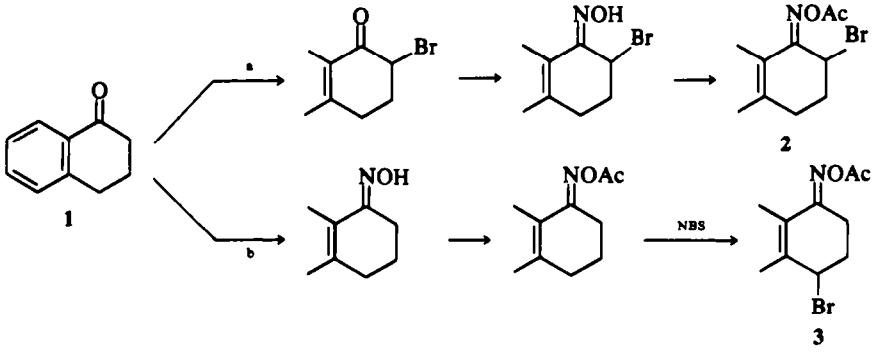


Scheme 1. From Ref. 14.

(i). Compound **4** was prepared from 4 - acetoxyimino - 1,2,3,4 - tetrahydro - phenanthrene by refluxing with N-bromosuccinimide (NBS) in carbon tetrachloride. Evidence for bromine at position 1 (and not at 3) comes firstly by analogy with the α-tetralone **1** series (Scheme 2) and secondly from the NMR-spectrum of **4**.

dimethylphosphate[22,23] in DMF under N_2. The reaction products (Scheme 3) were isolated by the combined procedures of column chromatography and preparative TLC. The yield of the identified reaction products (**5–14**) together represented 70% of the total yield.

Compounds **6**,[24] **8**[25] and **10**[26] were identified from



Scheme 2

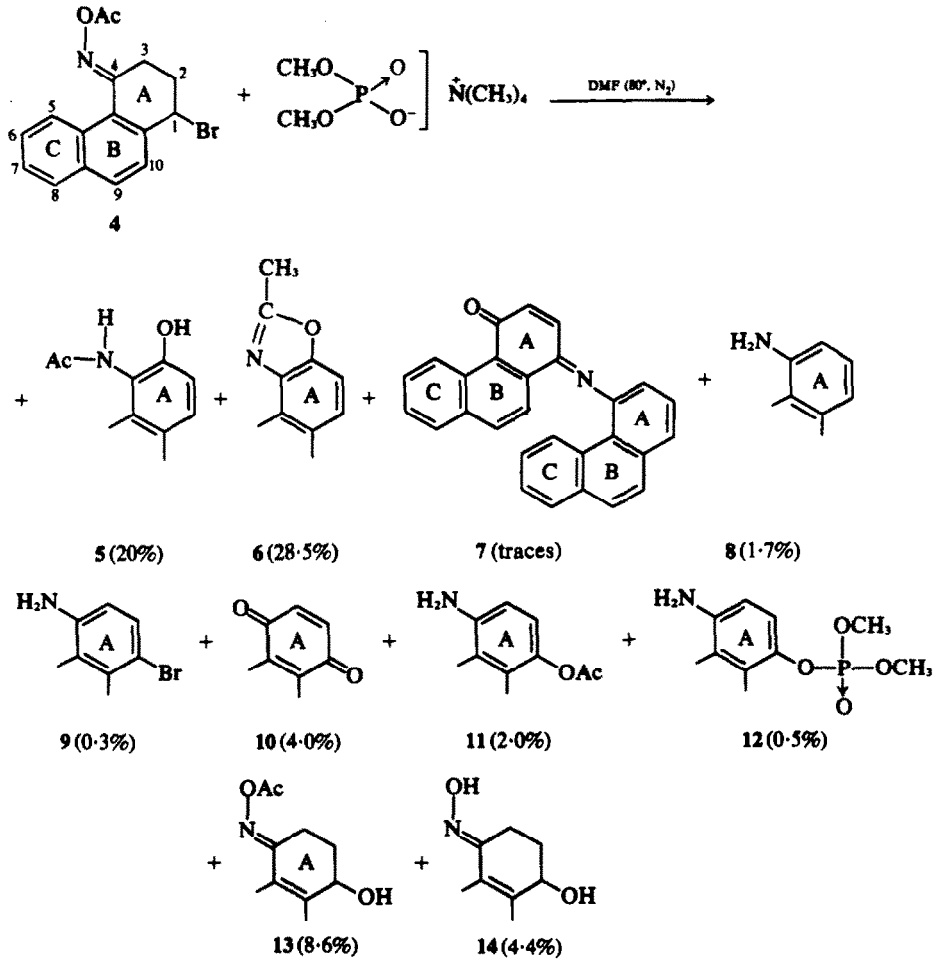
The reported synthesis of **2**[20,21] is designated (path a) in Scheme 2. Path b was used by us for the preparation of **3**. Compounds **2** and **3** (both found and calculated *m/e* 281/283) had different m.p. and IR spectra. The NMR spectrum of **2** gave signals for both H at C-4 at 2·23 (ax) and 2·74 ppm (ep); **3** gave signals for both H at C-2 at 2·9 (ax) and 3·27 ppm (eq). The NMR spectrum of **4** showed a signal at 3·3 ppm (corresponding to the 3·27 ppm signal of **3**).

We consider our failure to prepare 3 - bromo - 4 - oximino - 1,2,3,4 - tetrahydrophenanthrene (in analogy to path a in Scheme 2) may be due to steric reasons.

Dehydrobromination of **4** was carried out by heating (2 hr at 80°) the compound with tetramethylammonium

reported m.p. and spectral data. **5** was converted to the known N,N,O - triacetyl - 4 - amino - 3 - phenanthrol.[24] **9** (found and calculated *m/e* 271/273) gave a positive Ehrlich reaction and 1 - bromo - phenanthrene on deamination.[27]

Compound **11** gave a positive Ehrlich reaction. Elemental analysis gave a result consistent with the molecular formula $C_{16}H_{13}NO_2$. The parent ion of its mass spectrum had *m/e* 251 (M^+). The IR spectrum showed bands characteristic of NH_2 (3330 and 3350 cm^{-1}) and ester (1745 and 1200 cm^{-1}). The assignment of the acetoxy group to the *para* position rather than to the *ortho* position, with respect to the amino group, was made on the basis that if the latter type of compound is formed it would be



Scheme 3

immediately converted to the stable oxazole. Additionally, these compounds have not been described in the literature.

The mass spectrum of **12** gave, in addition to the parent peak *m/e* 371 (Calc. and Found), a characteristic peak at $M^+ - 109$, indicating elemination of a fragment $PO(OCH_3)_2$. **12** gave a positive Ehrlich reaction and its IR spectrum exhibited absorption bands characteristic of NH_2 (3340 and 3400 cm^{-1}), P=O (1275 cm^{-1}) and P–O–CH_3 (1180 cm^{-1}). The –$OPO(OMe)_2$-residue was assigned to the *para* position with respect to the amino group, on the finding that **9**, **10** and **11** are also *para* substituted; this preference may be due to steric reasons. **13** and **14** were identified by spectral data and by synthesis from 1 - acetoxy - 4 - acetoxyimino - 1,2,3,4 - tetrahydrophenanthrene.

The structures of **13**, **14** and **7** are discussed in Part II.

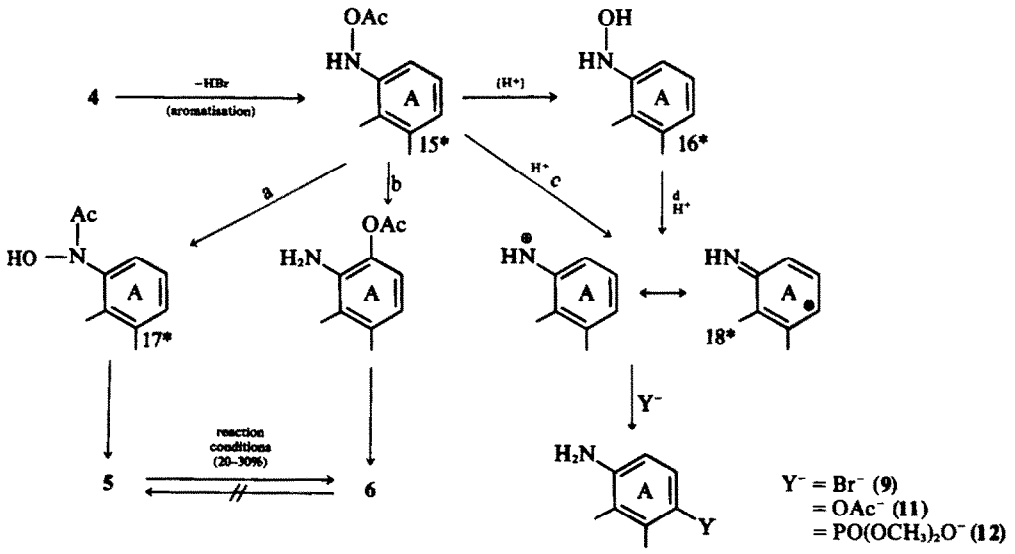
The possible mechanism of the origin of compounds **5**, **6**, **9**, **11** and **12** is represented in Scheme 4.

According to Scheme 4, the desired O - acetyl - 4 - hydroxylamino - phenanthrene **15** could be formed by dehydrohalogenation of **4**. Moreover, **15** is not stable under the acidic conditions of the reaction and is rapidly converted to other compounds.

Path a. The well known rearrangement of O - acyl - hydroxylamines to hydroxamic acids supports the idea that this path can be taken for intermediate **17**, which gives compound **5** in acidic conditions by Bamberger rearrangement.[28] It is possible that **5** could also be formed from **6**, as the conversion of methyl - 1 - napthoxazol to 1 - acetamino - 2 - naphthol under mild acidic hydrolysis has been reported.[29]

To verify this **6** and **5** were heated separately under our reaction conditions. **6** was found to be stable, while **5** was converted to **6** to the extent of 20–30%. This cyclisation may be sterically favoured with the elimination of water. This further strengthens the origin of **5** through path a.

Path b. Because the conversion of **5** and **6** under experimental conditions is only 20–30%, **5** can not be considered as the only source for the formation of **6** which has been isolated as a major product. Path b could be taken on the basis that arene hydroxylamine - O - sulfonic



Scheme 4

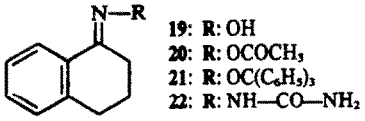
*Numbers with asterisks: not isolated compounds.

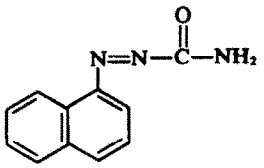
acid, through intramolecular rearrangement,[30,31] or as an intimate ion pair,[32] gives *ortho* substituted sulfonic acid derivatives.†

Path c, d. **9**, **11** and **12** may be formed from ion **18** which in turn may be formed from intermediates **15** or **16**. **10** could arise from the oxidation and hydrolysis of 4 - amino - 1 - phenanthrol during column chromatography on silica gel; the amino-phenanthrol may be formed by the attack of H_2O on **18** or by hydrolysis of **11**.

Nucleophilic replacement of bromine of **4** by dimethylphosphate or acetate and subsequent hydrolysis can give **13**, and further hydrolysis **14**.

(ii). Attempts at preparing **15** by dehydrogenation of 4 - acetoxyimino - 1,2,3,4 - tetrahydro - phenanthrene using a variety of quinones and conditions, failed. These included dichloro-dicyanobenzoquinone (DDQ), bromanil, or chloranil in solvents benzene, dioxane or anisole, at room temperature or on refluxing.





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Similarly attempts to dehydrogenate the oxime of α-tetralone **19** and its O-derivatives **20** and **21** were also without success. **19** with DDQ in equivalent amount in benzene at room temp after 2–3 days gave α-tetralone as the major product. **20** and **21** always gave starting material. Dehydrogenation resulted only in **22** when it was refluxed with DDQ in ethyl acetate. The possible mechanism of this dehydrogenation is described elsewhere.[33]

†Work is in progress to elucidate this mechanism.

EXPERIMENTAL

All m.ps are uncorrected. Spectroscopic equipment employed: Gilford UV spectrometer – 240, IR-spectrometer, Perkin-Elmer-225 (KI pellets), Varian-Associate-HA 100-NMR-spectrometer (solvent $CDCl_3$, δ-values, TMS as internal standard), Varian MAT - Ch - 7 - mass - spectrometer. Silica gel Merck 70-230 mesh ASTM was used for column chromatography. The TLC plates used for preparative separation were kieselgel F 254 (Merck), C, 2·5 mm thick (20 × 20 cm). UV-quenching compounds were detected under the UV-lamp.

Synthesis of 1 - *bromo* - 4 - *acetoxyimino* - 1,2,3,4 - *tetrahydro* - *phenanthrene* **4**. 5 g 4 - acetoxyimino - 1,2,3,4 - tetrahydrophenanthrene (5 g) and equal amount of NBS in 400 ml dry CCl_4 with traces of benzoylperoxide was refluxed for 3 hr, then cooled, filtered and the solvent removed under vacuum. The residue from benzene and light petroleum (70–80°) gave crystals, m.p. 108–9°, yield 81%; λ_{max} (dioxane) 255 (ϵ 36 000), and 316 nm (8 000); IR (cm^{-1}) 1760, 1200 (ester); 948 (N-O); NMR: H-5 9·22 (1, part of an ABCX system), H-6–H-10 7·2–8·9 (5), H-1 5·55 (1) t, J = 3 Hz (tentatively bromo axial), H-3 3·1–3·6 (2) m, H-2 2·1–2·7 (2) m, CH_3–CO– 2·33 (3) s; MS: M^+ 331/333, M^+ –HBr 252, M^+-CH_3COOH 271/273 (Found: C, 57·04; H, 4·05; N, 4·00; $C_{16}H_{14}BrNO_2$ requires: C, 57·83; H, 4·22; N, 4·22%).

Synthesis of 2 - *bromo* - 1 - *acetoxyimino* - 1,2,3,4 - *tetrahydronaphthalene* **2**. This was obtained from the correspond-

ing oxime by treatment with Ac_2O, m.p. 112°, yield 95%; λ_{max} (EtOH) 266·5 nm (ϵ 12 000); IR (cm^{-1}): 1775, 1206 (ester); 950 (N-O); NMR: H-8 8·17 (1) (a part of ABCX system); H5–H7 7·1–7·5 (3), H-2 5·60 (1) t, J *ca.* 3 Hz (bromo tentatively axial), H-3 2·05–2·45 (2) m, H-4 ax 2·23 (1) (a part of ABMX-system), J_{MX} = 17 Hz, J_{AX} = 5 Hz, J_{BX} = 11 Hz, H-4 eq 2·74 (1) (part of ABMX-system), J_{MX} = 17 Hz, CH_3C=O 2·27 (3) s. MS: M^+ 281/283, M^+-ketene 239/241, M^+-HBr 159.

Synthesis of 4 - *bromo* - 1 - *acetoxyimino* - 1,2,3,4 - *tetrahydro* - *naphthalene* **3**. This was prepared from the corresponding 1-acetoxyimino derivative by the method used for **4**, m.p. 124°, yield 60%; IR (cm^{-1}): 1765, 1200 (ester); 950 (N-O); 770 (4 aromatic H adjacent); NMR: H-8 8·19 (1) (part of ABCX-system), H-5 – H-7 7·2 – 7·5 (3), H-4 5·50 (1) t, J *ca.* 3 Hz (bromo tentatively axial), H-2 ax 2·9 (1), J_{gem} 18 Hz, $J_{ax/ax}$ 11 Hz, $H_{ax/eq}$ 5·5 Hz, H-2 eq, 3·27 (1), J_{gem} 18 Hz, $J_{eq/eq}$ 6 Hz, $J_{eq/ax}$ 3 Hz, H-3 2·0 – 2·65 (2)m, CH_3–C=O 2·29 (3) s; MS: M^+ 281/283, M^+-ketene 239/241, M^+-HBr 159.

Dehydrobromination of 1 - *bromo* - 4 - *acetoxyimino* - 1,2,3,4 - *tetrahydrophenanthrene* **4**. **4** (2 g) and tetramethylammonium-dimethylphosphate (3 g) in dry DMF (50 ml) was heated at 80° for 2 hr under N_2. The mixture was cooled and filtered, the residue obtained, after removal of the solvent from the filtrate, was suspended in water and extracted with ether. After drying the ether was removed from ether extract and the residue dissolved in 30 ml benzene. On TLC this soln gave spots with R_f 0·04 (**5**), 0·12 (**13** and **14**), 0·28 (**11**), 0·37 (**10**), 0·45 (**8** and **9**), 0·49 (**2**), 0·57 (**2**), 0·59 (**7**) and 0·63 (**6**) (benzene/EtOAc 9:1).

Isolation of 4 - *acetamino* - 3 - *phenanthrol* (**5**). The benzene soln obtained above gave on cooling a crystalline product, m.p. 168–70°, 300 mg (**5**), λ_{max} (EtOH): 230 (ϵ 29 000), 253 (50 000), 303·5 (11 000) and 361 nm (2 700); IR (cm^{-1}) 3320 (N-H), 3150 (OH), 1660 (amide I), 1528 (amide II). MS: M^+ 251, M^+-H_2O base peak. **5** was converted to its N,N,O-triacetyl - 4 - amino - 3 - phenanthrol by heating with NaOAc and Ac_2O, m.p. 170–1°,[24] MS: M^+ 335. The mother liquor, after isolating **5** was chromatographed on silica gel (150 g) and 180 fractions, of 15 ml each were collected. Fractions 1–135 were eluted with benzene and 136 to 180 with chloroform.

Isolation of 2 - *methyl* - (*phenanthreno* - 4'.3'.4.5 - *oxazol*) (**6**). Fractions 14–17: the residue was crystallized from benzene, m.p. 151–2° (lit. 151–3°)[24] 290 mg recovered; λ_{max} (EtOH). 221 (ϵ 39 000), 254 (52 000), 263 (59 000), 275 (24 000), 290 (17 000), 297 (5 500), 312 (830), 337·5 (3 500), 351 (1 300) and 354 nm (4 400), IR (cm^{-1}): 1600 (–C=N–), 1210 (–C–O); NMR: H-1, H-2, H-5–H-10 7·4–8·0 (8), CH_3–CO– 2·78 (3) s; MS: M^+ 233.

Isolation of 1 - *bromo* - 4 - *aminophenanthrene* **9**. Fractions 18–22: were combined and extracted with 2 N HCl. The acidic extract was made basic with Na_2CO_3 and extracted with ether. The ether extract was dried and solvent removed, the residue gave brownish crystals from light petroleum, m.p. 67°, (5 mg recovered). λ_{max} (dioxane): 232 (ϵ 31 000), 250 (28 000), 289 (19 000) and 374 nm (3 000); IR (cm^{-1}): 3375, 3300 (d, N-H); MS: M^+ 271/273, M^+-HBr 191.

Isolation of N - (4' - *phenanthryl*) - 1,4 - *phenanthrenequinone* - 1 - *imine* **7**. The combined fractions 18–22 after the isolation of **9** were neutralized by washing, solvent removed and the residue dissolved in light petroleum (70–80°). On cooling, a crystalline compound separated and was identified as **6** (110 mg). **7** was isolated as a red violet compound from the mother liquor by preparative TLC (benzene als solvent). MS: M^+ 383, M^+-HCO 354. Further data will be given in Part II of the series.

Isolation of 4 - *aminophenanthrene* **8**. The procedure adopted for the isolation of this compound from the combined fractions 23–32, was the same as for **9**. The residue from light petroleum gave crystals (**8**), m.p. 62–63° (Lit. 62–63°)[25]; λ_{max} (dioxane): 240 (ϵ 27 000), 248 (29 000), 266·5 (18 000), 284·5 (20 000), 353 (3 000), and 366·5 nm (3 000); IR (cm^{-1}): 3380, 3300 (d, N-H); MS: M^+ 193.

Isolation of phenanthrene-quinone-(1,4) (**10**). Fractions 34–80: **10** was isolated from the combined fractions by preparative TLC, and crystallized from light petroleum, m.p. 156. (lit. 155)[26]; λ_{max} (dioxane) 225 (ϵ 48 600), 258 (16 800), 278·5 (16 300), 288·5 (15 900), 362 (3 900) and 402 nm (2 300); IR (cm^{-1}): 1654 (>C=O); NMR: H-5 9·52 (1) (part of ABCX-system): H-2, H-3 6·94 (2) s; H-6–H-10 7·6–8·1 (5). MS: M^+ 208, M^+-CO 180, 180-CO 152.

Isolation of 1 - *hydroxy* - 4 - *acetoxyimino* - 1,2,3,4 - tetrahydrophenanthrene (**13**). Fractions 136–166: The residue from benzene gave crystals of **13**, m.p. 171–3°, (140 mg recovered); λ_{max} (dioxane): 225·5 (ϵ 35 000), 240 (26 000), and 309·5 nm (10 000); IR (cm^{-1}): 3460 (OH), 1740, 1215 (ester), 940 (N-O); NMR: H-5 9·16 (1) (a part of ABCX-system), H-6–H-10 7·4–8·0 (5), H-1 4·91 (1) dd, $J_{1,2ax}$ 6 Hz. $J_{1,2eq}$ 4 Hz, H-2 1·98–2 (2) m, H-3 3–3·4 (2) m, CH_3–C=O– 2·32 (3) s, 1-OH 1·88 (1) s. MS: M^+ 269, M^+-ketene 227.

Isolation of 1 - *hydroxy* - 4 - *hydroxyimino* - 1,2,3,4 - *tetrahydro* - *phenanthrene* **14**. Fractions 167–180: The residue from benzene gave colourless crystals, m.p. 199–200°; (60 mg recovered); λ_{max} (dioxane): 234·5 (ϵ 45000) and 304·5 nm (10 000), IR (cm^{-1}): 3200 (broad-OH), 938 (N-O); NMR: H-5 9·13 (1) (part of ABCX-system), H-6–H-10 7·1–8·3 (5), H-2 1·95–2·1 (2) m, H-3 2·9–3·3 (2) m, H-1 4·93 (1) t. MS: M^+ 227, M^+–OH 210.

Isolation of 4 - *amino* - *phenanthryl* - 1 - *acetate* (**11**) *and* 4 - *amino* - *phenanthryl* - 1 - *dimethylphosphate* (**12**). The mother liquors after the isolation of **13** and **14**, giving a positive reaction with Ehrlich's reagent, were combined, and on TLC two Ehrlich positive spots were resolved with R_f 0·46 and 0·07 (benzene/EtOAc 75:25). Both compounds were separated by preparative TLC. The compound of R_f 0·46 was crystallized from light petroleum, m.p. 94–5° and identified as **11**; λ_{max} (dioxane): 230·5 (ϵ 34 000), 238 (30 000), 247·5 (32 000), 287 (20 000) and 307 nm (7 000); IR (cm^{-1}): 3420 and 3350, (d, N-H), 1745, 1200 (ester); MS: M^+ 251, M^+-ketene (209) (Found: C, 76·25; H, 5·07; N, 5·23. $C_{16}H_{13}NO_2$ requires: C, 76·49; H, 5·18, N, 5·57%). The second compound with R_f 0·07, was a brownish viscous substance and could not be crystallized. A pure sample for spectral analysis was obtained by repeated preparative TLC and identified as **12**: λ_{max} (dioxane): 217·5 (ϵ 29 000), 230 (33 000), 238 (31 000), 247·5 (33 000), and 287 nm (19 000); IR (cm^{-1}): 3400, 3340 (d, N-H), 1275 (P=O), 1230 (P-O-C-aromate), 1180 (POMe); MS: M^+-$PO(OCH_3)_2$ 208.

Synthesis of trityl ether (**21**). To a vigorously stirred soln of 1 - hydroxyimino - 1,2,3,4 - tetrahydronapthalene (1 g) and triethylamine (1 ml) in DMF (2 ml), tritylchloride (1·73 g) was added in one step and stirring continued for 1 hr. The mixture was then allowed to stand for 24 hr. This was then poured into water and stirred until it solidified, filtered and the solid washed with water, 1·89 g. On TLC (benzene $CHCl_3$ 1:1) three spots were resolved R_f 0·15, 0·26 and 0·59 (major). The compound with R_f 0·59 was purified by passage through a silicagel column using benzene as solvent. Colourless crystals were obtained from benzene/light petroleum solution, m.p. 153°, yield 65%; λ_{max} (EtOH): 260 (ϵ 16 000), 264 (16 000), and 288 nm (5 300); IR (cm^{-1}): 937 (N-O); NMR: H-5–H-7 and 15 phenyl-H 6·95–7·5 (18); H-8 7·62 (1) (part of ABCX-system): H-2 and H-4 2·6–3·05 (4) m, H-3 1·85-2 (2) m. MS: A peak of molecular ion could not be obtained. The highest peak was at *m/e* 260 probably of trityl carbinol (Found: C, 86·31; H, 6·25; N, 3·48; $C_{29}H_{25}NO$ requires: C, 86·35; H, 6·20; N, 3·47%).

Dehydrogenation of 1 - *semicarbazone* - 1,2,3,4 - *tetrahydro* - *naphthalene* (**22**). **22** (100 mg) with 1·5 mole equiv. DDQ was refluxed for 6 hr in EtOAc (50 ml). Solvent was removed and the residue dissolved in $CHCl_3$ and chromatographed on a silica gel column (100 g). A yellow band was eluted with chloroform, and on crystallization from benzene gave reddish crystals, m.p. 135–7°, (15 mg recovered) and was identified as **23**, λ_{max} (EtOH): 217·5 (ϵ 67 000), 256 (14 000) and 361 nm (7 600); IR (cm^{-1}): 3390, 3220 (d,

N-H), 1710 (>C=O), 1570 (-N=N-, very weak); MS: M^+ 199, M^+-$CONH_2$ 155.

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