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ATTEMPTS TO PREPARE AROMATIC O-ACYL-HYDROXYLAMINES—III

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Abstract—From the reaction mixture of the dehydrobromination of 1 - bromo - 4 - benzoyloxyimino - 1,2,3,4 - tetrahydrophenanthrene (1) with 1,8-diazabicyclo [5.4.0] undec-7ene (DBU) in benzene and in heavy atom solvents several products were isolated and their structures elucidated. The origin of the majority of compounds has been considered via the labile O-benzoylhydroxylamine **12**, except product **11**. The generation of a nitrenium ion in singlet state 13a may be responsible for the formation of **4a,b, 5a,b, 6a,b, 7** and **8** (path a). A Bamberger rearrangement of **12** (path b) explains the generation of **9a,b** and **10**, a hydrolysis of **12** (path c) and following reactions may yield **8** while homolytic cleavage and dimerization of the new radical **21** explains the formation of **3a,b**.

INTRODUCTION

Carcinogenic aromatic amines and amides when metabolically activated to O-acylhydroxylamines *in vivo* at target tissues, generate nitrenium ions.[1-3] It is expected that these electrophilic species, when initially generated, are most likely to be in singlet state and can undergo intermolecular insertion reactions with tissue nucleophiles. But some of the nitrenium ions may undergo spin inversion to triplet state and in such state they are likely to dehydrogenate or oxidize the tissue nucleophiles. For sometime we have been interested to attempt to synthesize aromatic O-acylhydroxylamines and to study the property of these reactive intermediates, including the generation and properties of nitrenium ions.[4-6] With this aim we now report our results of the dehydrobromination of 1 - bromo - 4 - benzoyloxyimino - 1,2,3,4 - tetrahydrophenanthrene **1** with DBU **2**, and the effect of heavy atom solvents on this reaction.

RESULTS AND DISCUSSION

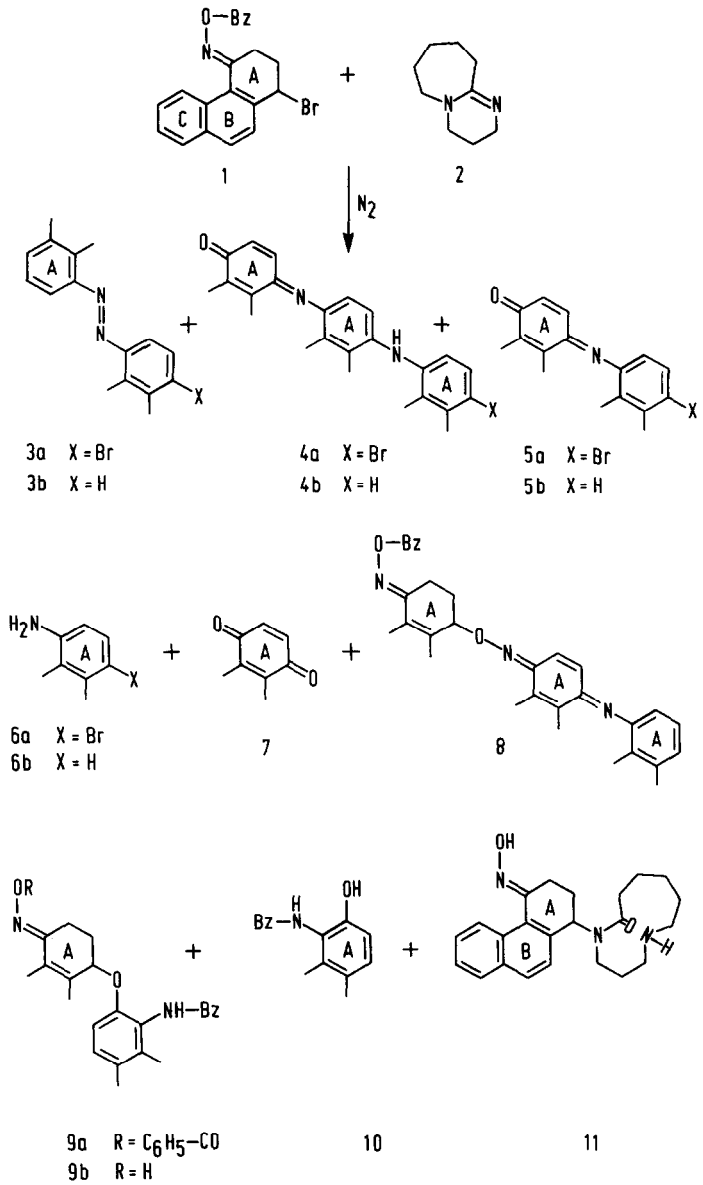
Dehydrobromination of **1** with DBU (2.5 mole equivalents) in benzene under nitrogen atmosphere yielded a mixture of products which were isolated by combined procedures of column chromatography and preparative tlc. Dehydrobromination of **1** with DBU was also carried out in methylene bromide or in benzene bromoform mixture. The compounds isolated and their structures are given in Scheme 1, the yields are summarized in Table 1.

CHARACTERIZATION OF PRODUCTS

Compounds **3a** and **3b** were reddish crystalline products. The MS of **3a** showed the molecular ion at *m/e* 460/462 and fragment ions at *m/e* 283 ($M-C_{14}H_9$) and *m/e* 205 ($M-C_{14}H_8Br$). The analogous data found for **3b** are *m/e* 382 (M^+), *m/e* 285 ($M-C_{14}H_9$) and *m/e* ($C_{14}H_9$). The IR of **3b** has characteristic C–H-stretching vibrations (3040 cm^{-1}) and in addition to this band **3a** shows C–Br-bands at 1250 and 650 cm^{-1}. On reductive cleavage 1-bromo-4-aminophenanthrene (**6a**) and 4-aminophenanthren (**6b**) were obtained. **4a** and **4b** were violet products, formulae $C_{42}H_{25}BrN_2O$ and $C_{42}H_{26}N_2O$ could be assigned from elemental analysis and MS, as described in the experimental part. Intense IR bands at 1640 cm^{-1} for **4a** and 1635 cm^{-1} for **4b** indicated the quinone carbonyl band. Products **5a, 5b, 6a, 6b** and **7** were identified as reported earlier.[5] **8** was a orange crystalline product, whose IR bands at 1735, 1622, 1250 and 940 cm^{-1} pointed for a = N–O–COC_6H_5-group. Its structure was proved when mild alkaline hydrolysis yielded the known[5] N⁴ - (4 - hydroxylimino - 1,2,3,4 - tetrahydro - 1 - phenanthryloxy) - N′ - (4 - phenanthryl) - 1,4 - phenanthrenquinonediimine. This again was converted to the known[5] acetoxyimino derivative by treating it with acetanhydride. Product **9a** was identified from its elemental analysis and spectroscopic data. IR indicated a secondary amide (1670 cm^{-1}) and again the presence of a benzoyloxyimino group, ^1H NMR showed the presence of 24 aromatic protons, therefrom δ 9.4 and δ 9.2

Table 1. Reaction of 1 and DBU (2) in different solvents (yields %)

	3a	3b	4a	4b	5a	5b	6a	6b	7	8	9a	9b	10	11	Total
Benzene	3.0	3.0	0.9	0.7	6.8	24.7	4.0	6.1	4.0	6.0	16.1	2.7	1.0	-	79.0
Methylene-bromide	2.0	2.0	-	-	-	-	5.5	5.1	3.8	-	18.1	6.0	0.5	10.4	53.4

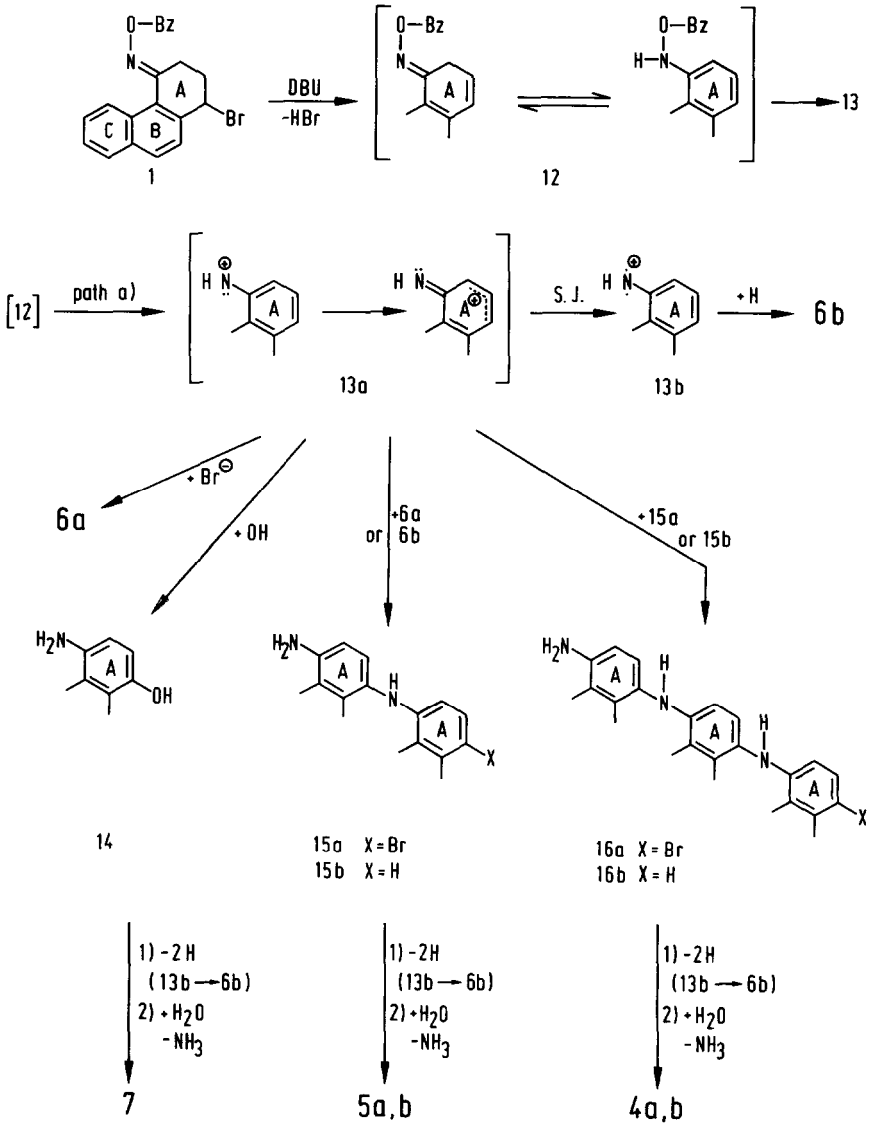


Scheme 1.

characteristic for H-5 and H-5′ respectively, and 5 cycloaliphatic protons. In MS the highest fragment appeared at *m/e* 313, which originates from the cleavage of the ether-bridge combined with the movement of a proton from the isocyclic ring to the oxygen. Thus two isomeric ions *m/e* 313 are formed. The nature of the fragment containing the phenolic hydroxyl is indicated by the loss of water (*m/e* 295) probably due to easy cyclization to a stable oxazole intermediate. Ions at *m/e* 208 (313-C_6H_5CO) and *m/e* 192 (313-C_6H_5–COO) are also consistent with the proposed structure. The correlation of **9b** to **9a** was established by benzoylation of **9b** to yield **9a**. Compound **10** again was identified by spectroscopic data. As described above the molecular ion at *m/e* 313 lost water to form probably an oxazol fragment *m/e* 295. The UV maxima at 230, 253 and 304 nm showed a bathochromic shift to 239, 260, 328 nm in the presence of alkali ^{1}H NMR showed 13 aromatic protons (δ –8.78 for H-5). The signal at δ 8.9 ppm, due to phenolic hydroxyl, disappeared after treatment with deuteriumoxid. Product **11** was assigned formula $C_{23}H_{29}N_3O_2$ from its elemental analysis and MS. Its MS gave M^+ at *m/e* 379 and other characteristic peaks were at *m/e* 363 (M^+–O), 362 (M^+–OH), 211, 210, 209 and 169. IR had bands for =NOH (3509–3333 broad, 940 cm^{-1}), –NH (3205 cm^{-1}) and C=O of lactam (1650 cm^{-1}). ^{1}H NMR indicated 6 aromatic protons (9.0 for H-5) and 21 aliphatic protons, an oxyimino-H (7.88 intensity 1), and the N–H proton buried under the aliphatic protons.

Mechanism

In analogy to our previous considerations[4-6] it is assumed that dehydrobromination proceeds via the intermediate formation of the labile, unisolated O-ben-

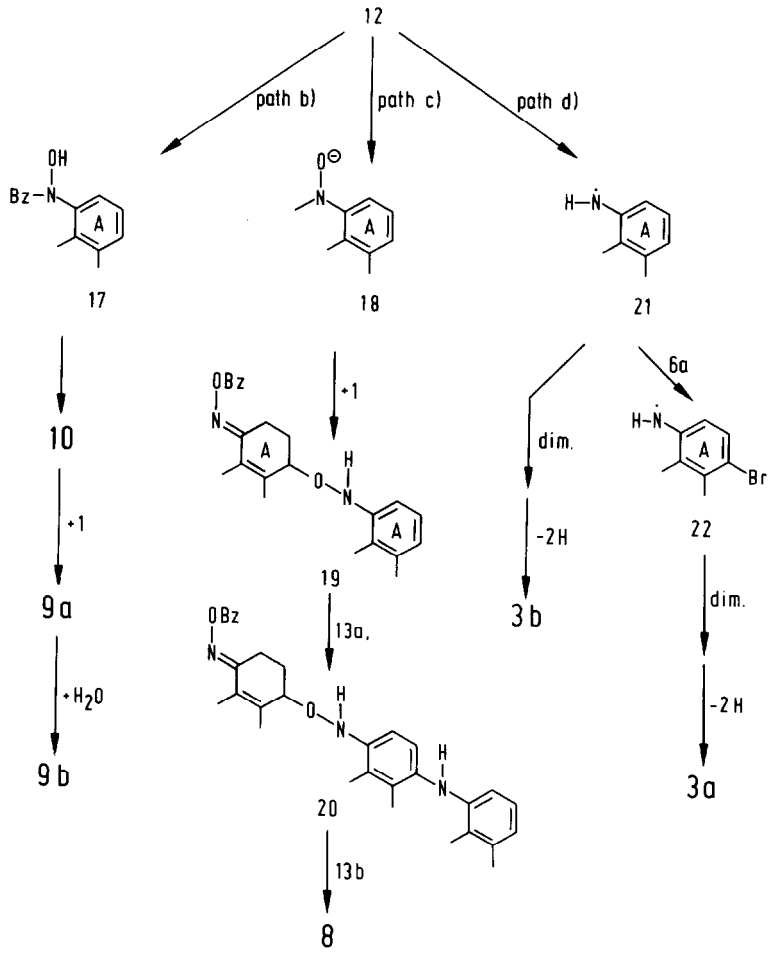


Scheme 2.

zoylhydroxylamine **12**. This intermediate is expected to undergo various fates: (a) generation of a nitrenium ion, (b) rearrangement to a hydroxamic acid, (c) hydrolysis to a hydroxylamine and (d) generation of a free radical through homolytic cleavage.

Path a. It is assumed that the nitrenium ion first generated is in singlet state (**13a**); nucleophilic attack by various species may form new products. Some of the nitrenium ions could get converted to the more stable triplet state (**13b**) and this may be used mainly as dehydrogenating agent during the complex reaction (Scheme 2). Thus the nitrenium singlet **13a** yield **6a** by nucleophilic attack of a bromide ion. Attack of a hydroxyl group forms the p-aminophenol analogue **14**. This may be dehydrogenated by **13b** to yield the corresponding quinonimine which is hydrolysed to form the stable phenanthrenequinone **7**. **6a,b** itself as a nucleophile may react with the nitrenium singlet **13a** to yield **15a,b** which on dehydrogenation and hydrolysis of the intermediate quinonimine is converted to **5a,b**. Now, using the intermediates **15a,b** as nucleophiles in the same manner as above, the isolation of **4a,b** in markedly lower yield is well understood. **6b** is the reaction product of the dehydrogenation reaction using **13b**. It is evident from the product distribution (Table 1) that some of the reaction products (**4a,b** and **5a,b**), the initial step for the formation of which is proposed to be through the singlet state **13a**, were found to be absent, when the reaction was performed in presence of heavy atom solvents. Heavy atom solvents are well known to convert singlet state molecules to its triplet state.[7,8]

Path b. From aqueous washings of the reaction mixture **10** was isolated. The formation of this N-benzoyl-o-aminophenol analog is easily understood to be the product of a Bamberger rearrangement[9] of the hydroxamic acid **17** which however was not found in the



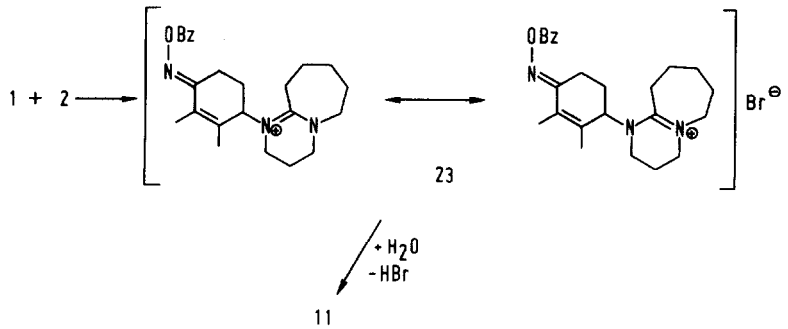
Scheme 3.

present case. **10** and **17** analogues have already been identified in the reaction of **1** (CH_3CO instead of C_6H_5CO) with DBU.[4,5] Under the prevailing basic conditions the anion of **10** may substitute the bromine in allylposition of **1** to form **9a**, which is hydrolized to yield **9b**.

Path c. The anion **18**, formed by hydrolysis of the not isolated O-benzoylhydroxylamine **12** may substitute the bromine in allylic position of **1** to yield **19**, which by electrophilic attack of **13a** (→**20**) and following dehydrogenation will generate **8**. This reaction sequence should not be possible in a heavy atom solvent because of the involvement of the nitrenium ion singlet **13a** as explained above; indeed **8** was not found in the reaction mixture of **1** and **2** in methylene bromide solution.

Path d. The proposed generation of **21** from **12** is in consistence with the homolytic cleavage of O-acylhydroxylamines.[11] **21** is expected to be sufficiently stable to dimerize to a hydrazo derivative which on further dehydrogenation may give **9b**. **21** also could generate another radical **22** and from this the formation of **3a** can be viewed as mentioned above.

For formation of **11** DBU (2) may substitute bromine in allylic position of **1** to form the immonium salt **23**



Scheme 4.

which may further get hydrolyzed to form **11** during work up procedure of the reaction mixture (Scheme 4). It is probably the first observation of this type of cleavage of DBU to form an eleven membered cyclic derivative.

EXPERIMENTAL

Instruments and materials are as given in Part I.[4]

1 - *Bromo* - 4 - *benzoyloxyimino* - 1,2,3,4 - *tetrahydrophenanthrene* (1). 4 - Benzoyloxyimino - 1,2,3,4 - tetrahydrophenanthrene (10 g, 0.03 mol) and N-Brominosuccinimide (NBS) (10 g) in 400 ml of dry carbon tetrachloride was refluxed for 2 hr together with traces of α,α'-azoisobutyronitrile. The reaction mixture was cooled and filtered, the solvent was removed under vacuum and the residue crystallized from benzene: 10 g (80%), m.p. 129–131°.

UV (EtOH) λ_{max} nm (ϵ): 247 (65,000), 316 (43,000). IR (KBr) 1735, 1615, 1200 and 940 cm^{-1} (benzoyloxyimino). ^1H NMR: $\delta = 9.55$ (m, 1H, H-5), 7.35–8.0 (m, 8H, H-6 to H-10, H-3 to H-5 of phenyl), 8.1–8.3 (m, 2H, H-2 & H-6 of phenyl), 5.55 (t, J = 3 Hz, 1H, H-1), 2.1–2.4 (m, 2H, H-2), 3.3–3.5 (m, 2H, H-3), MS (70 eV) *m/e*: 393/395 (M^+), 271/273 ($M-C_6H_5$–COOH), 105 (C_6H_5–CO).

Dehydrobromination of 1 *with DBU.* To a soln of 1 (5.00 g, 12 mMol) in dry benzene (200 ml) DBU (5.00 g, 35 mMol) in dry benzene (50 ml) was added dropwise under nitrogene atmosphere and the reaction was allowed to stand for 20 hr at room temperature. The crystalline product which separated (DBU.HBr) was filtered off and the filtrate was washed neutral to litmus with distilled water (5 × 100 ml). The combined aqueous washings were kept for the isolation of **10**. The organic layer was dried and the solvent removed under reduced pressure. The residue on tlc analysis gave spots; R_f 0.6 (**3a, 3b**), 0.58 (**4a, 4b**), 0.50 (**5a**), 0.48 (**6a**), 0.45 (**5b**), 0.42 (**6b**), 0.33 (**7**) and 0.12 (**8**) (solvent : benzene); R_f 0.65 (**3a, 3b**), 0.63 (**4a, 4b**), 0.55 (**5a**), 0.52 (**6a**), 0.50 (**5b, 6b**), 0.46 (**7**), 0.35 (**8**), 0.25 (**9a**) and 0.21 (**9b**) (solvent : benzene–ethyl acetate 9 : 1).

The residue was dissolved in benzene and chromatographed on a silica gel column (350 g) and eluted with a gradient petrol ether–benzene, benzene, benzene–ethyl acetate, 65 fractions each of 50 ml were collected and the fractions with the same R_f were pooled.

Fractions 3–10. The reddish residue on tlc (petr.ether–benzene 1 : 1) indicated two spots of R_f 0.65 (**3a**) and 0.56 (**3b**). Using this solvent system both products were separated by preparative tlc.

1 - *Bromo* - 4,4' - *azophenanthrene* (3*a*). 88 mg reddish yellow crystals (from petr.ether–benzene) m.p. 205–207°. UV (dioxane) λ_{max} nm (ϵ): 241 (50,000), 271.5 (24,000), 291.5 (2000), 367 (5000). IR (KBr): 1620 (–N=N–) cm^{-1}, 1250, 520 (C–Br). MS (70 eV) *m/e*: 460/462 (M^+), 283/285 ($M-C_{14}H_9$). Reductive cleavage: a small quantity of **3a** was suspended in ethanol–water containing sodium hyposulphite and refluxed until the colour discharged. The solvent was removed, the residue treated with sodium hydroxide solution and extracted with ether. The organic layer was dried, the solvent was removed and the residue on tlc gave Ehrlich positive spots according to the R_f value identical with those of 1-bromo-4-aminophenanthrene (**6a**) and 4-aminophenanthrene (**6b**).

4,4'-*Azophenanthrene* (3*b*). 74 mg reddish yellow crystalls from (petr.ether–benzene) m.p. 163–165°. UV (dioxane), λ_{max} nm (ϵ): 239 (7000), 270 (34,000), 283 (31,000), 298 (25,000), 363 (7500). IR (KBr): 1625 cm^{-1} (–N=N–), MS (70 eV) *m/e* : 382 (M^+), 205 ($M-C_{14}H_9$), 177 ($C_{14}H_9$). Reductive cleavage, done as with **3a** gave 4-aminophenanthrene (**6b**).

Fractions 11–18. The violet residue on tlc (petr.ether) indicated two spots with R_f 0.53 (**4a**) and 0.49 (**4b**) which were separated by preparative tlc.

N - [1 - (1 - *Bromophenanthr* - 4 - *ylamino*)*phenanthr* - 4 - *yl*] - 1,4 - *phenanthrenequinone* - 1 - *imine* (**4a**). 26 mg violet crystalls (from petr.ether–benzene) m.p. 235–238°. UV (MeOH)λ_{max} nm (ϵ): 206 (80,000), 233 (70,000), 297 (32,000), 334 (21,500). IR (KBr): 1640 cm^{-1} (C=O). MS (70 eV) *m/e*: 652/654 (M^+), 382 ($M-C_{14}H_9BrN$). (Found: C, 77.01, H, 3.91; N, 4.22. $C_{42}H_{25}BrN_2O$ requires: C, 77.18, H, 3.82, N, 4.28%).

N - [1 - (*Phenanthr* - 4 - *yl* - *amino*)*phenanthr* - 4 - *l*] - 1,4 - *phenanthrenequinone* - 1 - *imine* (**4b**). The violet residue (16 mg) could not be crystallized. IR (KBr): 1635 cm^{-1} (C=O). MS (70 eV) *m/e* 594 (M^+), 382 ($M-C_{14}H_{10}N$), 367. (Found: C, 87.68, H, 4.50, N, 4.71. $C_{42}H_{26}N_2O$ requires: C, 87.80, H, 4.53, N, 4.87%).

Fractions **19–24**: 1 - *Bromo* - *N* - (4 - *phenenthryl*) - 1,4 - *phenanthrenequinone* - 1 - *imine*. (**5a**, 200 mg) and 1 - bromo - 4 - aminophenanthrene (**6a**, 140 mg) were separated by preparative tlc (petroleumehter–benzene 1 : 1) and identified as described.[5]

Fractions **25–33**: *N* - (4 - *phenanthryl*) - 1,4 - *phenanthrenequinone* - 1 - *imine*. (**5b**, 600 mg) and 4 - *aminophenanthrene* (**6b**, 150 mg) were separated by preparative tlc (petroleumether–benzene 1 : 1) and identified as described.[5]

Fractions **35–38**: *Phenanthrenequinone* - 1,4 (7). 106 mg was isolated and identified as described earlier.[4]

Fractions **40–45**: N^4 - [4 - (*Benzoyloxyimino*) - 1,2,3,4 - *tetrahydro* - 1 - *phenanthryloxyl*] - N^1 - (4 - *phenanthryl*) - 1,4 - *phenanthrenequinone* - *diimine* (**8**). 180 mg orange crystalls (from benzene–petr.ether) m.p. 168–170°. UV (MeOH) λ_{max} nm (ϵ): 224 (105,000), 245 (77,000), 300 (39,500). IR (KBr): 1735, 1622, 1250 and 940 cm^{-1} (benzoyloxyimino). Alkaline hydrolysis: 20 mg **8** was allowed to stand in alcoholic potassium hydroxide for two hours at room temperature. Ethanol was removed, the aqueous suspension was neutralized with diluted HCl and extracted with ether. The organic layer was dried, the residue on crystallisation from benzene gave reddish crystals, m.p. 208°–210° and was identified by mixture melting point, R_f and IR as N^4 - [4 - hydroxyimino - 1,2,3,4 - tetrahydro - 1 - phenanthryloxyl - N^1 - (4 - phenanthryl)] - 1,4 - phenanthrene quinone - diimine.[5]

Fractions **47–56**: 1 - (4 - *Benzamido* - 3 - *phenanthryloxy*) - 4 - *benzyloxyimino* - 1,2,3,4 - *tetrahydrophenanthrene* (**9a**). The residue on crystallization from benzene gave 640 mg colourless crystalline product, m.p. 193–194°. UV (MeOH) λ_{max} nm (ϵ): 209 (95,000), 228 (76,000), 249 (84,000), 254 (87,600), 304 (25,000). IR (KBr) 3280 (NH), 1720, 1620, 1260, 940 (benzyloxyimino), 1670 and 1510 cm^{-1} (amide). ^1H NMR ($CDCl_3$) $\delta = 7.3$–7.8 (m, 22H, aromatic H). 9.4 (m, 1H, H-5), 9.2 (m, 1H, H-5); 5.64 (broad 1H, H-1), 3.3 (m, 2H, H-3), 2.2–2.4 (m, 2H, H-2) MS (70 eV) *m/e*: 313, 295 (313-H_2O), 208 (313-C_6H_5CO), 192 (313-$C_6H_5CO_2$). (Found: C, 80.31; H, 4.80; N, 4.38. $C_{42}H_{30}N_2O_4$ requires: C, 80.51, H, 4.79, N, 4.45%).

Fractions **57–63**: 1 - (4 - *Benzamido* - 3 - *phenanthryloxy*) - 4 - *hydroxyimino* - 1,2,3,4 - *tetrahydrophenanthrene* (**9b**). The residue (90 mg) was crystallized from benzene, m.p. 204–205°. IR (KBr) 3400 (–OH), 3300 (–NH), 1670 (amide I) and 1510 (amide II) cm^{-1}. Benzoate derivative of **9b**: 20 mg of **9b** was shaken with benzoyl chloride in 10% NaOH (aq.). The crude product was filtered, dried and crystallized from benzene, m.p. 193–194° and was identified as **9a** by tlc in different solvent systems, by mixture melting point and by superimposable IR.

4 - *Benzamido* - 3 - *phenanthrol* (**10**). The aqueous washings of the reaction mixture were acidified in presence of ice and ether. The etheral organic layer was washed with 0.5% aqueous sodium carbonate and water, dried, the solvent was evaporated and the residue crystallized from benzene to give 40 mg, m.p. 207–208°. UV (MeOH) λ_{max} nm (ϵ): 206 (26,500), 230 (44,000), 253 (51,000), 304 (11,500), 343 (1800), 362 (2300). UV (MeOH + 0.1 N NaOH) λ_{max} nm: 239, 260, 328 nm. IR (KBr): 3600–3300 (broad, OH), 3250 (–NH), 1640 and 1530 (amide). ^1H NMR ($CDCl_3$) $\delta = 8.78$ (m, 1H, H-5), 8.07 (m, 2H, H-2 and H-2 of phenyl), 7.3–7.9 (m, 10H, H-6 to H-10, H-1 and H-2 of Phenanthryl- H-3 to H-5 of phenyl), 8.91 (s, 1H, phenol-OH, exchangeable with deuterium oxide). MS (70 eV) *m/e* 313 (M^+), 295 (m-H_2O), 208 (M-C_6H_5CO), 105 (C_6H_5CO).

1 - (1,5 - *Diaza* - 11 - *oxocycloundecan* - 1 - *yl*) - 4 - *oxyimino* - 1,2,3,4 - *tetrahydrophenanthrene* (**11**). 11 was isolated from the last six fractions (**59–65**) from the silica gel column by elution with chloroform–methanol (9.1). The residue gave 500 mg white crystalline product (from benzene) m.p. 160–161°. UV (MeOH) λ_{max} nm (ϵ): 236 (54,000) 304 (15,500). IR (KBr): 3500–3300 (broad, OH), 3150 (NH), 1650 (C=O), 1200, 940 (–N–O) cm^{-1}. ^1H NMR ($CDCl_3$): $\delta = 9.0$ (m, 1H, H-5), 7.3–7.9 (m, 5H, H-6 to H-10), 21 aliphatic H, therefrom 4.03 (t, J = 5 Hz, 1H, H-1 equatorial), 1.4–3.5 (m, 20H, cycloaliphatic H). MS (70 eV) *m/e* 379 (M^+), 363

(M–O), 362 (M–OH), 225, 209, 195, 180, 169, 140. (Found: C, 72.71; H, 7.67; N, 11.02. $C_{23}H_{29}N_3O_2$ requires: C, 72.82, H, 7.64; N, 11.08%).

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