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Synthesis of Phenanthro[9,10-d]oxazoles from 10-(Methoxyimino)phenanthrene-9-one

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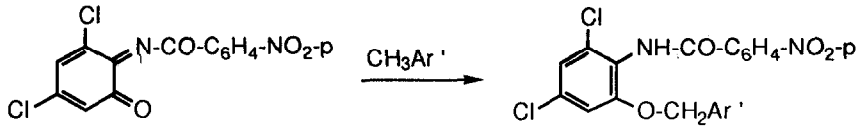
Abstract: 10-(Methoxyimino)phenanthren-9-one **3** easily reacts with the methyl substituted aromatics **4(a-d)**, as well as with α-bromo-p-xylene **6** and the α-substituted methyl derivatives **7(a-i)**, to afford in 5-64% yield the corresponding 2-aryl substituted phenanthro[9,10-d]oxazoles **5(a-g)**, most probably via a free radical reaction sequence. In several cases the unsubstituted oxazole **12** is also obtained, while reaction of compound **3** with the N-methyl substituted amines **7g** and **14(a,b)** leads to the aminooxazoles **13** and **15(a,b)** respectively.

Pfundt and Hardham[1] reported in 1965 that photolysis of phenanthrene-9,10-quinone monoimine in the presence of substituted toluenes leads to phenanthro[9,10-d]oxazoles. It is assumed that intermediates arising from a homolytic scission of the aryl C-H bond are involved in this remarkable transformation[2]. Recently we reported[3] that 10-(methoxyimino)phenanthren-9-one **3** reacts thermally with substituted oxazoles of type **5** in 9-58% yield. Furthermore, we found[3] that treatment of **3** with dimethylacetylene-dicarboxylate (DMAD) in refluxing toluene affords the phenyloxazole **5f**, as well as both 7-oxo-7H-dibenzo[de,g]quinoline-4,5-dicarboxylate, obtained by a Diels-Alder cycloaddition of the dienophile across the heterodiene system -C=C-C=N-OCH_3 of **3**, and 2-phenyldibenzo[f,h]quinoline-3,4-dicarboxylate, obviously a product of further cycloaddition of the same dienophile to the 2-aza-1,3-butadiene system HO-C=C-N=C(Y)Ar of the intermediate **11** (Y=H, Scheme **4**), followed by elimination of water. It should be noticed that compound **5f** was obtained in considerably shorter time[3] by reaction of benzyl bromide instead of toluene with **3**. Treatment[3] of **3** with N-methylpyrrole led to formation of 12% of the unsubstituted oxazole **12**. Almost simultaneously, *Heine et al.* reported[4] that N-(2,4-dichloro-6-oxo-2,4-cyclohexadien-1-ylidene)-4-nitrobenzamide **1** reacts at room temperature with 9,10-dimethylanthracene as well as with hexamethylbenzene to afford high yields of the corresponding ethers **2** (Scheme **1**).

The work detailed in this paper involves extension of the above described reactions of compound **3** by use of several other methylaromatic or α-susbstituted methylaromatic systems, including benzylamines, as well as of N-methylanilines, in order to shed more light on the mechanistic pathway, that leads in all cases to formation of phenanthro[9,10-doxazole derivatives.

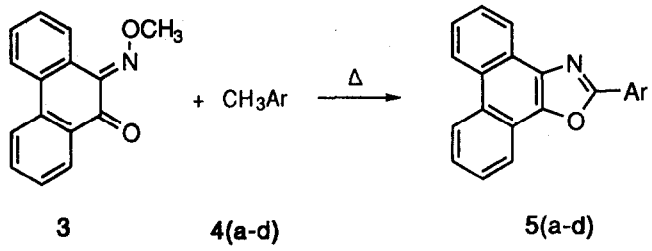


1 2

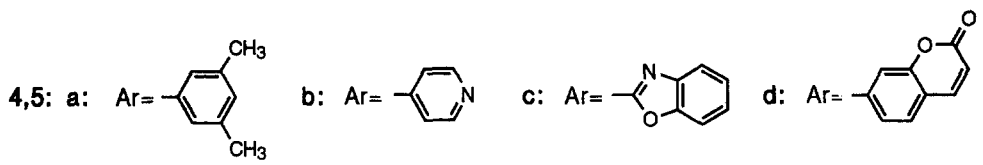
Scheme 1

RESULTS AND DISCUSSION

The products obtained from the reactions of **3** with the methylaromatic systems **4(a-d)** are depicted in Scheme 2. Usually the reactions were carried out by refluxing a solution of **3** in compound **4**, which also served as a solvent. Products **5a**[1], **5b**[5], **5c** and **5d** were obtained respectively in 37%, 5%, 26% and 11% yield. Only the monooxazole derivative **5a** was obtained from the reaction with mesitylene.

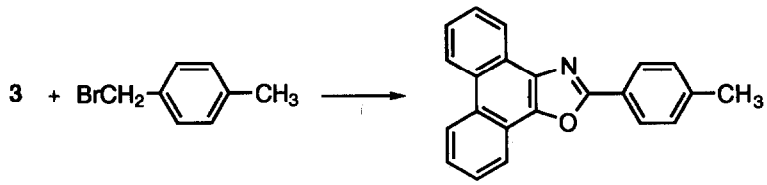


3 4(a-d) 5(a-d)



Scheme 2

Reaction of α-bromo-p-xylene **6** with compound **3** led to formation of 15% of the known[3] 2-(p-tolyl)-phenenthro[9,10-d]oxazole **5e** (Scheme 3), proving that the bromomethyl substituent of compound **6** is in this case more reactive than the methyl substituent. Although expected as well, 2-(p-bromobenzyl)phenenthro[9,10-d]oxazole was never detected in the reaction mixture. Obviously, elimination of HBr instead of H_2 accompanies this oxazole ring formation[3].



6 5e

Scheme 3

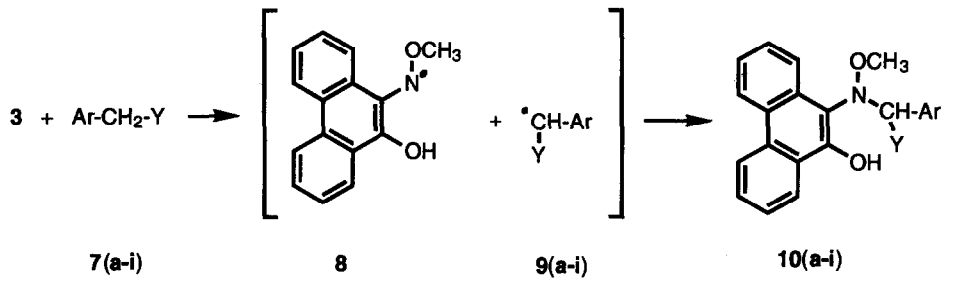
Relying on the above mentioned fact, we further investigated the reactivity of substituted methyl groups towards the quinone monoimine **3** by studying reactions of the latter with compounds **7(a-i)**, bearing a $-CH_2Y$ moiety. The reactants used, the reaction conditions applied and the products obtained are presented in Table 1 and Scheme **4**.

Table 1

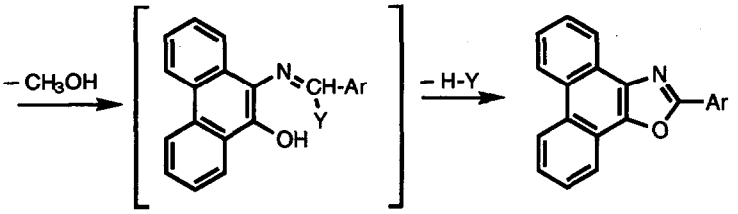
Experimental Data for Reactions between Compounds **7(a-i)** and **3**

	Compound **7**		Reaction Conditions		Products
	Ar	Y	Temp. °C	Time	obtained (%)
7a	C_6H_5	-OH	205	3h	**5f**[6] (48)
7b	C_6H_5	$-OCOCH_3$	180	2.5h	**5f** (23)
7c	C_6H_5	-SH	193	35 min	**5f** (24), **12**[3] (15)
7d	C_6H_5	$-COC_6H_5$	140	3h	**5f** (64), C_6H_5COOH (87)
7e	C_6H_5	$-COCH_3$	185	2h	**5f** (60)
7f	C_6H_5	$-NH_2$	184	1.5h	**5f** (45), $C_{21}H_{14}N_2$ (14)
7g	C_6H_5	$-(CH_3)_2$	180	20 min	**5f** (28), **12** (7), **13** (10)
7h	$4\text{-}CH_3OC_6H_4$	-OH	130	1.5h	**5g**[7] (48)
7i	$4\text{-}C_6H_4N$	-OH	145	5h	**5b** (47), **12** (27)

The liquid state of most compounds **7** allowed them furthermore to act as solvents, while in the case of **7d**, a solid, the reaction mixture was melted. The corresponding 2-aryl-phenanthro[9,10-d]oxazole **5** was isolated as sole or main product in all cases being, formed in yields varying from 23 to 64%. In contrast to the poor 5% yield of **5b** obtained from the reaction of **3** with 4-picoline **4b**, use of 4-hydroxymethylpyridine **7i** afforded 47% of the heterocycle **5b**, whereas there was observed a noteworthy increase in the yield of **5f** when the substituent Y was $-COCH_3$, $-COC_6H_5$ or -OH. Furthermore, of considerable mechanistic interest was the isolation of the unsubstituted oxazole **12** from the reaction of **3** with compounds **7c**, **7g** or **7i**, that of benzoic acid in the case of compound **7d** and that of the oxazole **13** when the amine **7g** is used.

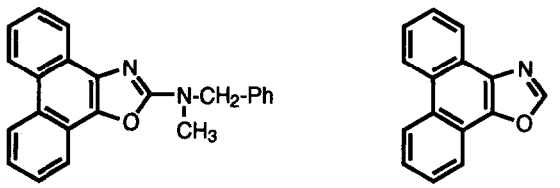


7(a-i) 8 9(a-i) 10(a-i)



11(a-i) 5(b, f, g)

5f: Ar= Ph
5g: Ar= C_6H_4-OCH_3-p



13 12

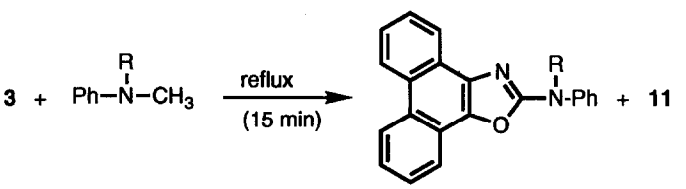
Scheme 4

The reaction mechanism depicted in Scheme **4**, similar to the one we have already[3] proposed for the reaction of **3** with compounds of the type Ar-CH_2Y (Y=H), can readily account for the formation of all the 2-substituted oxazoles. The suggested formation of a hydroxy-intermediate of type **10** rather than of an ether derivative of type **2** (Scheme 1) was further supported by subsequent transformation of the former into an imine intermediate of type 11 and its trapping by dimethyl acetylenedicarboxylate[3]. Elimination of a H-Y molecule from the intermediate 11 leads to the corresponding oxazoles **5**. Relying upon the experimental data presented in Table 1, this elimination should proceed homolytically, since a uniform explanation for the formation of all oxazoles **5** obtained cannot be possibly supported by a polar elimination of H-Y in the cases of -$COCH_3$ and -COC_6H_5. The higher yield of **5f**, observed in both cases where the above mentioned groups are concerned, is in good agreement with their higher free-radical

stability. Further oxidation of the benzaldehyde eliminated from compound **11d** could account for the benzoic acid isolated in this reaction. The suggested homolytic scission of the O-H and C-Y bonds of the intermediates **11** to form the final product **5** is also supported by the fact that **11c** (Y= SH) and **11f** (Y= NH_2) did not afford thiazole or imidazole derivatives respectively, *via* elimination of water, most probably because homolytic elimination of the H-Y moiety gives rise to stabler radicals in the rest of the intermediates **11**, favouring thus the formation of the oxazole **5f**.

Product $C_{21}H_{14}N_2$, m.p. 237-9 °C, obtained from the reaction of compound **3** with benzylamine **7f** remains unidentified, since its m.p. and spectral data (IR, ^1H NMR, MS) differ significantly from those recorded on an authentic sample of 2-phenyl-1H-phenanthro[9,12-d]imidazole (m.p. 312-4 °C), prepared according to literature procedures[8], as well as from the literature data[9] of another probable candidate, 3-phenyl-1(2)H-dibenz[e,g]indazole [m.p. 252-3 or 245-6 °C, IR 3200 cm^{-1} (νNH)]. The isolation of the unsubstituted compound **12** in several of the reactions studied prompted us to examine the possibility of its formation by thermal dehydration of **3**. The mechanistic pathway would involve an initial thermal isomerization of **3** to the corresponding N-methylnitrone[10], subsequent transformation of the latter to the o-hydroxy-N-methylidene-N-oxide, further intermolecular cyclization to N-hydroxy-2H-phenanthro[9,10-d]oxazole and final dehydration to **12**. However, heating of **3** in p-nitrobenzene or quinoline at 150 °C for 5h and then to 190 °C for 12h did not lead to the expected compound. Obviously, further evidence is necessary to explain the formation of the unsubstituted oxazole **12**.

The reaction of **2** with N,N-dimethylbenzylamine **7g** furnished three oxazole derivatives, *e.g.* compounds **5f** and **12**, as well as the rather unexpected 2-(N-methyl-N-benzyl)aminophenanthro[9,10-d]oxazole **13**. The formation of the latter is probably due to a mechanism similar to the one proposed in Scheme **4**, but involving participation of a methyl group of the amine in the reaction sequence, instead of its N-methylene moiety, and leading thus to **13** *via* elimination of CH_3OH and H_2. Although this process is less hindered, oxazole **5f** is formed in higher yield than oxazole **13**, in obvious agreement with the lower stability of the free radical assumed to act as the intermediate in the last case.



14(a,b) **15(a,b)**

14, 15: a: R= H
b: R= CH_3

Scheme 5

The forementioned easy preparation of a 2-aminosubstituted oxazole from the monoxime **3** prompted us to investigate reactions of the latter with several other N-methyl substituted amines. Preliminary experiments demonstrated that compound **3** reacts smoothly with both N-methyl-aniline and

N,N-dimethylaniline to afford the corresponding 2-(N-phenyl)aminophenanthro[9,10-d]oxazole **15a** (19%) and 2-(N-methyl-N-phenyl)aminophenanthro[9,10-d]oxazole **15b** (7%) respectively. The unsubstituted derivative **12** was also obtained in the first case in 18% yield (Scheme **5**).

The observations noted above show that the previously studied[3] reactions of **3** with methyl-substituted aromatics can be considerably extended. In fact, interaction of **3** with further similar systems, usually α-substituted ones, or with N-methylanilines affords in all cases the corresponding phenanthro[9,10-d]oxazole derivatives, most probably *via* a homolytic reaction sequence.

EXPERIMENTAL

M.ps. are uncorrected and were determined on a Kofler hot-stage apparatus. IR spectra were obtained with a Perkin-Elmer 297 spectrophotometer as Nujol mulls. ^{1}H NMR spectra were recorded with deuteriochloroform as solvent on a Bruker Model AW 80 (80 MHz) spectrometer with TMS as the internal standard. Mass spectra were determined on a TS 250 VG mass spectrometer. The ionization energy was maintained at 70 eV.

Reaction of 10-(Methoxyimino)phenanthren-9-one **3** *with* **4a**. *Preparation of 2-(3,5-xylyl)-phenanthro[9,10-d]oxazole* **5a**. A solution of **3** (0.355 g, 1.5 mmol) in mesitylene (1 mL) was refluxed for 1h and then column chromatographed on silica gel (dichloromethane) to afford **5a** (0.179 g, 37%), m.p. 269-70 °C (from light petroleum-dichloromethane) (lit.[1] m.p. 266-8 °C).

Reaction of **3** *with* **4b**. *Preparation of 2-(4-pyridyl)-phenanthro[9,10-d]oxazole* **5b**. A solution of **3** (0.355 g, 1.5 mmol) in 4-methylpyridine (1 mL) was refluxed for 2h and then column chromatographed on silica gel (light petroleum-ethyl acetate 1:2) to afford **5b** (0.022 g, 5%), m.p. 254-6 °C (from light petroleum-dichloromethane) (lit.[5] m.p. 249-51 °C).

Reaction of **3** *with* **4c**. *Preparation of 2-(2-benzoxazolyl)-phenanthro[9,10-d]oxazole* **5c**. A solution of **3** (0.355 g, 1.5 mmol) in 2-methylbenzoxazole (5 mL) was heated at 130 °C for 72 h and then column chromatographed on silica gel (light petroleum-dichloromethane 1:10 up to 2:1) to afford **5c** (0.131 g, 26%), m.p. 269-70 °C (from light petroleum-dichloromethane); IR ν_{max}: 1625, 1610, 1580, 1520 cm^{-1}; ^{1}H NMR δ_H: 7.33-8.05 (4H,m), 8.57-8.93 (4H,m). MS m/z: 336 (M^+, 100%), 237 (25), 180 (14), 164 (28), 151 (13). Analysis calc. for $C_{22}H_{12}N_2O_2$ (336.33): C, 78.57; H, 3.57; N, 8.33. Found: C, 78.28; H, 3.50; N, 8.12.

Reaction of **3** *with* **4d**. *Preparation of 2-(7-coumarinyl)-phenanthro[9,10-d]oxazole* **5d**. A mixture of 0.355 g, (1.5 mmol) of **3** and 0.239 g (1.5 mmol) of 7-methylcoumarine was heated at 140 °C for 7 h and then column chromatographed on silica gel (light petroleum-dichloromethane 1:3 up to 1:20) to afford **5d** (0.060 g, 11%), m.p. > 300 °C (from ethyl acetate); IR ν_{max}: 1735, 1605, 1575, 1560 cm^{-1}. MS m/z: 363 (M^+, 100%), 335 (12), 164 (46). Analysis calc. for $C_{24}H_{13}NO_3$ (363.35): C, 79.33; H, 3.58; N, 3.85. Found: C, 79.20; H, 3.48; N, 3.68.

Reaction of **3** *with* **6**. *Preparation of 2-(4-methylphenyl)-phenanthro[9,10-d]oxazole* **5e**. A solution of **3** (0.355 g, 1.5 mmol) in α-bromo-p-xylene (1 mL) was refluxed for 5 h and then column chromatographed

on silica gel (light petroleum-dichloromethane 10:1 up to 1:3). The appropriate fraction was further separated by preparative t.l.c. on silica gel (light petroleum-ethyl acetate 20:1) to afford **5e** (0.068 g, 15%), m.p. 244-6 °C (from dichloromethane) (lit.[1] m.p. 246-8 °C).

*Reaction of **3** with **7a**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f**.* A solution of **3** (0.355 g, 1.5 mmol) in benzylalcohol (1 mL) was refluxed for 3 h and then column chromatographed on silica gel (light petroleum-ethyl acetete 5:1) to afford **5f** (0.212 g, 48%), m.p. 204-5 °C (from dichloromethane-methanol) (lit.[6] m.p. 205-6 °C).

*Reaction of **3** with **7b**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f**.* A solution of **3** (0.355 g, 1.5 mmol) in benzylacetate (1 mL) was heated for 2.5 h at 180 °C and then column chromatographed on silica gel (light petroleum-dichloromethane 5:1) to afford **5f** (0.102 g, 23%).

*Reaction of **3** with **7c**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f** and phenanthro[9,10-d]oxazole **12**.*. A solution of **3** (0.355 g, 1.5 mmol) in benzyl mercaptan (1 mL) was refluxed for 35 min and then column chromatographed on silica gel (light petroleum-dichloromethane 5:1) to afford **5f** (0.106 g, 24%) and subsequently **12** (0.049 g, 15%), m.p. 148-9 °C (from ethanol) (lit.[3] m.p. 145-6 °C).

*Reaction of **3** with **7d**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f**.* A solution of **3** (0.355 g, 1.5 mmol) in benzylphenylketone (1 mL) was heated for 2 h at 140 °C and then column chromatographed on silica gel (light petroleum-ethyl acetate 5:1) to afford **5f** (0.283 g, 64%) and benzoic acid (0.158 g, 87%).

*Reaction of **3** with **7e**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f**.* A solution of **3** (0.355 g, 1.5 mmol) in benzylmethylketone (1 mL) was heated for 2 h at 185 °C and then column chromatographed on silica gel (light petroleum-ethyl acetate 5:1) to afford **5f** (0.265 g, 60%).

*Reaction of **3** with **7f**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f** and compound $C_{21}H_{14}N_2$.* A solution of **3** (0.355 g, 1.5 mmol) in benzylamine (1 mL) was refluxed for 1.5 h and then column chromatographed on silica gel (light petroleum-ethyl acetate 5:1) to afford **5f** (0.199 g, 45%) and the unidentified compound $C_{21}H_{14}N_2$ (0.062 g, 14%), m.p. 237-9 °C (from light petroleum-dichloromethane); IR ν_{max}: 2850, 1600, 1575, 1530, 1510 cm^{-1}; ^1H NMR δH: 5.82 (1H,s), 7.04-7.49 (7H,m), 7.59-7.78 (3H,t), 7.86-8.08 (1H, d), 8.62-8.91 (2H,q). MS m/z: 294 (M^+, 37%), 293 (100), 190 (54), 163 (11).

*Reaction of **3** with **7g**. Preparation of 2-phenyl-phenanthro[9,10-d]oxazole **5f**, phenanthro[9,10-d]oxazole **12** and 2-(N-methyl-N-benzyl)aminophenanthro[9,10-d]oxazole **13**.* A solution of **3** (0.355 g, 1.5 mmol) in N,N-dimethylbenzylamine (1 mL) was refluxed for 20 min and then column chromatographed on silica gel (dichloromethane) to afford **5f** (0.124 g, 28%), **12** (0.023 g, 7%) and **13** (0.051 g, 10%), obtained by further separation of the appropriate fraction by preparative chromatography on silica gel (light petroleum-dichloromethane-ethyl acetate 2:10:1), m.p. 174-5 °C (from light petroleum-dichloromethane); IR ν_{max}: 1630, 1605, 1540 cm^{-1}; ^1H NMR δ_H: 3.23 (3H,s), 4.88 (2H,s), 7.17-7.78 (8H,m), 7.94-8.83 (5H,m). MS m/z: 338 (M^+, 87%), 247 (100), 219 (63), 177 (23), 151 (19). Analysis calc. for $C_{23}H_{18}N_2O$ (338.39): C, 81.65; H, 4.14; N, 8.25. Found: C, 81.48; H, 4.28; N, 8.11.

*Reaction of **3** with **7h**. Preparation of 2-(4-methoxyphenyl)-phenanthro[9,10-d]oxazole **5g**.* A solution of **3** (0.355 g, 1.5 mmol) in 4-methoxybenzylalcohol (1 mL) was heated for 1.5 h at 130 °C and then column chromatographed on silica gel (light petroleum-ethyl acetete 5:1) to afford **5g** (0.185 g, 38%), m.p. 226-7 °C (from light petroleum-dichloromethane) (lit.[7] m.p. 222-3 °C)

*Reaction of **3** with **7i**. Preparation of 2-(4-pyridyl)-phenanthro[9,10-d]oxazole **5b** and phenantrho[9,10-d]oxazole **12**.* A mixture of **3** (0.355 g, 1.5 mmol) and **7i** (0.218 g, 2 mmol) was heated for 5 h at 140 °C and then column chromatographed on silica gel (light petroleum-dichloromethane 5:1 up to 1:2) to afford **5b** (0.207 g, 47%) and **12** (0.089 g, 27%).

*Reaction of **3** with **14a**. Preparation of 2-(N-phenyl)aminophenanthro[9,10-d]oxazole **15a**.* A solution of **3** (0.237 g, 1 mmol) in 0.25 mL N-methylaniline was refluxed for 15 min and then column chromatographed on silica gel (dichloromethane-ethyl acetate 10:1) to afford **15a** (0.058 g, 19%), m.p. 198-9 °C (from light petroleum-dichloromethane); IR ν_{max}: 3150, 1645, 1605, 1540 cm^{-1}; ^1H NMR δ_H: 6.95-7.94 (8H,m), 8.33-8.93 (5H,m). MS m/z: 310 (M^+, 100%), 77 (12). Analysis calc. for $C_{21}H_{14}N_2O$ (310.34): C, 81.26; H, 4.55; N, 9.03. Found: C, 81.08; H, 4.28; N, 8.88.

*Reaction of **3** with **14b**. Preparation of 2-(N-methyl-N-phenyl)aminophenanthro[9,10-d]oxazole **15b**.* A solution of **3** (0.237 g, 1 mmol) in 0.25 mL N,N-dimethylaniline was refluxed for 15 min and then column chromatographed on silica gel (dichloromethane-ethyl acetate 10:1) to afford **15b** (0.023 g, 7%), m.p. 122-4 °C (from ethanol); IR ν_{max}: 1640, 1615, 1600, 1560 cm^{-1}; ^1H NMR δ_H: 3.71 (3H,s), 7.16-8.14 (9H,m), 8.32-8.94 (4H,m). MS m/z: 324 (M^+, 100%), 309 (11), 281 (17), 219 (10), 177 (12). Analysis calc. for $C_{22}H_{16}N_2O$ (324.36): C, 81.48; H, 4.93; N, 8.64. Found: C, 81.30; H, 5.00; N, 8.48.

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