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NEW SYNTHETIC ROUTE TO 9,10-IMINO-PHENANTHRENE†

J. N. DENIS and A. KRIEF*
Department of Chemistry, Facultés Universitaires N. D. de la Paix 61, rue de Bruxelles, B-5000 Namur, Belgium

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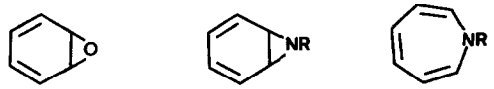
Abstract—The synthesis of 9,10-imino-phenanthrene is performed in two steps from phenanthrene. N-alkylation using Michael type reaction is also disclosed.

Recognition of carcinogenic properties of arene oxides **1** has led to increasing interest in biochemical[1], chemical[2] and theoretical field[3] as well as discovery of new synthetic routes to such reactive molecules. The nitrogen analogs **2** are much less known[4] and many of them show a high tendency to exist in the azepin form **3**.[2a,3b,5] Compounds **2** and **3** are generally in equilibrium and its position is of course dependent on the nature of the corresponding arene and of the substituant directly attached to the nitrogen atom.



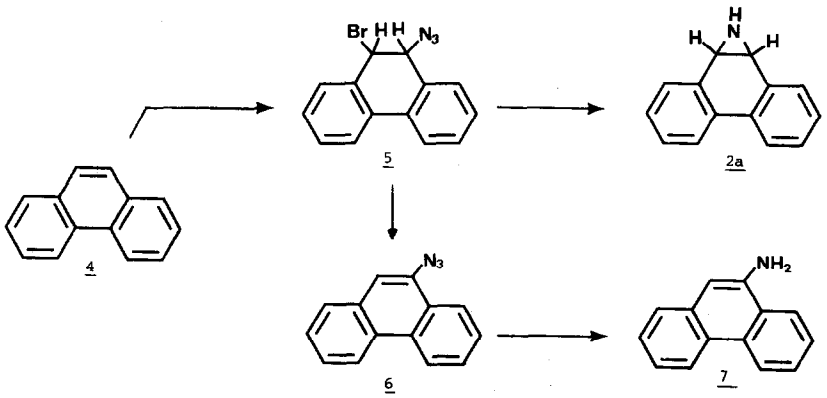
1 2 3

The completely unknown chemical and biological properties of arene-imines **2** and the lack of general synthetic routes to such compounds led us to devise a new approach to these derivatives which requires the synthesis of unknown *nitrogen unsubstituted arene imine* **2** (R = H) from the arene itself and further introduction of electron-attracting or electron-donating group on the N atom. Phenanthrene was chosen as a good candidate for such approach. A recent report[6] which discloses the synthesis of 9,10-imino-phenanthrene, our key intermediate, prompts us to present our own results in this field, especially the first unambiguous proof in favour of an arene imine structure for 9,10-imino-phenanthrene **2a**.

The synthesis of **2a** presented in Scheme I takes advantage of the easy addition of bromine azide to the more nucleophilic 9,10 C=C double bond of phenanthrene **4** which occurs in nitromethane[7] and allows the synthesis of 9-bromo-10-azido-9,10-dihydrophenanthrene **5** in 50% yield. However, we were not able to synthesise such compound when bromine azide is prepared *in situ* according to our procedure[8] (NBS, NaN_3 in DME/water). The low nucleophilicity of phenanthrene probably allows the rapid destruction of the BrN_3, once formed, by the competiting reaction of the water present.

9-Bromo-10-azido-9,10-dihydrophenanthrene **5** is a stable compound which was stored for several years without any appreciable decomposition but which is very rapidly transformed in 70% yield to 9-azidophenanthrene **6** by addition of silica gel (SiO_2 Merck 7733) to its pentane solution. Interestingly this reaction does not occur if ether is substituted to pentane.

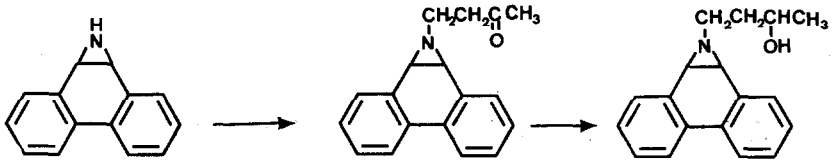
We found that 9-bromo-10-azido-9,10-dihydrophenanthrene **5** is readily transformed to the desired 9,10-iminophenanthrene **2a** when reacted



4 5 2a 6 7

Scheme I.

† These results were first disclosed at the 4th Symposium on Heterocyclic Chemistry held in Louvain-la-Neuve (Belgium), in July 1978.



2a 8 9

Scheme II.

with excess lithium aluminium hydride in THF (4 eq, -15°; 0.5 hr; 61% yield). 9-aminophenanthrene **7** (4% yield) and phenanthrene (19% yield) are also formed in this reaction and removed from the aziridine **2a** by preparative layer chromatography. We were rather surprised at the high termal stability of **2a** which is recovered (~90%) after heating in THF for 6hr.

Physicochemical data (^1H and ^{13}C NMR; MS, IR, UV) agree with the proposed aziridine structure for **2a**; for example, the two benzylic protons resonate (^1H NMR) as a singlet at 3.56 ppm ($CDCl_3$)[6], the NH proton absorbs at 0.6 ppm (exchanged by addition of D_2O) and the two C atoms part of the aziridine resonate (^{13}C NMR), as expected, as a singlet at 38.05 ppm (broad band decoupled) and furthermore the coupling constant J_{C-H} : 176 Hz is similar to that described for other aziridines.[9]

And last but not least, the results of an X-ray monocrystal diffraction* at R = 0.20 already disclose to presence of the 3-membered heterocycle in **2a** (distance between C_9 and C_{10} C atoms: 1.70 Å and C_9-N-C_{10} angle: 65°).

The first alkylations performed with methyl iodide or benzyl bromide in neutral or basic media were disappointing since they led in each case to several unidentified products in which the aziridine ring was absent.

Successful alkylation was however achieved by triethylamine catalysed addition reaction on methyl vinyl ketone (Scheme II). The resulting N-(3-oxobutyl)-9,10-epiminophenanthrene **8** obtained in 60% yield was further reduced in 80% yield to the corresponding alcohol **9** by lithium aluminium hydride.

Finally we have taken the opportunity of the easy formation of 9-azidophenanthrene **6** to propose its high yield (83%) reduction to 9-aminophenanthrene (Scheme I).

The biological activity of 9,10-iminophenanthrene is under investigation† at the National Cancer Institute (USA).

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* Refer to the refinement of the structure already reached. Better refinement is in progress at Laboratoire de Chimie Physique Moléculaire, Facultés Universitaires N. D. de la Paix. The authors thank G. Evrard, B. Norberg and F. Durant for the X-ray analysis (results to be published).

† Dr. R. B. Inge (National Institute of Health) is acknowledged for the biological testing of compound **2a**.

EXPERIMENTAL

Infrared data were obtained using a "Perkin Elmer" model 257 spectrophotometer; the spectra are reported in cm^{-1} and *UV spectra* were recorded on a Pye Unicam SP 1800 spectrophotometer. *Proton magnetic resonance (^1H NMR)* spectra were performed on a Jeol M.H. 100 spectrometer, 100 MHz using tetramethylsilane (TMS) as an internal standard and the signals are expressed in parts per million downfield from the standard. ^{13}C NMR spectra were performed on a Brucker W.P. 60 spectrometer in deuterochloroform (TMS as internal standard). *Mass spectra and exact mass determination* were obtained on an A.E.I. model MS 30 spectrometer. All melting points (mp) were determined on a Kofler hot plate and are uncorrected.

Microanalysis were performed in Paris (Service de Microanalyse, Université Pierre et Marie Curie, Paris VI) by Mr. Dorme who is greatly acknowledged. *Layer chromatography (Tlc) : Analytical thin layer chromatography* was performed on pre-made, glass backed plate: SiO_2 60 PF_{254}, 250 microns (Merck-5719) or Al_2O_3 150 F_{254} (typ.T), 250 microns (Merck 5732). Compounds were visualized by UV illumination and by heating to 150° after spraying 5% phosphomolybdic acid in ethanol. *Preparative layer chromatography (Plc)* were performed on pre-made glass backed plate: Al_2O_3 150 F_{254} (Typ.T), 1,5 mm (Merck 5726) or on SiO_2 plates prepared as follow: 440 g. of silica gel (Merck 7747) (for fifteen 20×20 cm plates) was shaken with 880 ml of distilled water to obtain a free-flowing slurry. Using a CAMAG 21602 automatic preparative spreader, the plates were covered with an even coating of adsorbent (1.5 mm). Just after coating, the plates are put down in a non ventilated closed hood with water saturated atmosphere (obtained by boiling water) for one hour. The hot water bath was removed after one hour and the plates are allowed to dry in the *closed* hood for 20 hr. The dried plates are activated (140°, 10 hr) prior use (>95% success on >10.000 plates prepared). Anhydrous THF and ether are distilled from sodium benzophenone ketyl just prior reaction.

9-Bromo-10-azido-9,10-dihydrophenanthrene **5.** Bromine azide in CH_2Cl_2 (140 ml, 70 mmol), [prepared according to Hassner[7] from Br_2 (11.2 g, 70 mmol), sodium azide (45.5 g, 700 mmol), HCL conc (28 ml), water (7 ml) and CH_2Cl_2 (140 ml), then decanted and dried over $MgSO_4$] is slowly added at −10° to a stirred soln of phenanthrene (7.12 g, 40 mmol) in nitromethane (110 ml). After 3 hr, the solvents are removed *in vacuo* and the solid residue recrystallized in ether leading to white crystals of **5** (6 g, 50% yield), mp 110-111°. IR($CHCl_3$) 2100(s), 1485, 1450, 1200, 1150 cm^{-1}; ^1H NMR ($CDCl_3$) δ 4.71 (d, J = 2 Hz, 1H), 5.21 (D, J = 2 Hz, 1H), 7.05-7.50 (m, 6H), 7.60-7.90 (m, 2H); MS(70 eV) *m/e* 301, 299(M^+), 259, 257(M^+-N_3), 193, 192, 191, 190, 179, 178, 177, 176, 166, 165, 164, 163, 152, 151, 150. Mol. Weight Calcd for $C_{14}H_{10}BrN_3$: 299.0058, 301.0039. Found: 299.0032, 301.0013; Anal. Calcd for $C_{14}H_{10}BrN_3$: C, 56.02; H, 3.36. Found: C, 56.30; H, 3.52.

9,10-Imino-phenanthrene **2a.** Compound **5** (3 g, 10 mmol) in THF (10 ml) is added to a stirred suspension of

$AlLiH_4$ (420 mg, 11 mmol) in anhyd THF (10 ml) and cooled to −15° the white-grey slurry is stirred at this temp for a further 0.5 hr then hydrolysed with water (2 ml) and extracted with chloroform. The organic layer was filtered through a celite pad, washed with water, brine, and dried over Na_2CO_3. The solvents were removed *in vacuo* and the crude product purified by plc (Al_2O_3), eluted with ether. The product with R_f 0.35 is recristallized in $CHCl_3$/pentane leading to **2a** (1.17 g, 61% yield), mp 162°–163° dec. Phenanthrene (R_f 0.78) and 9-aminophenanthrene (R_f 0.60) were isolated respectively in 19% and 4% yield. **2a** : IR($CHCl_3$) 3270, 2950, 1480, 1450, 1375 cm^{-1}. ^1H NMR ($CDCl_3$) δ 0.6 (m, 1H), 3.56 (s, 2H), 7.20–8.20 (m, 8H). ^{13}C NMR ($CDCl_3$) δ: 130.32, 129.27, 128.07, 127.92, 126.42, 123.80 (C, aromatics) 38.20(*C*HNH). UV λ_{max} (ϵ) ($CHCl_3$) 272 shoulder (s) (17900), 278(s) (19200), 282 (20400), 288(s) (14900), 294(s) (11300), 305 nm (5500); MS (70 eV) (relative intensity) *m/e* 193 (M^+, 100), 192(7.5), 178(5.9), 176(2.7), 166(15.6), 165(46.2), 164(6.0), 163(6.2), 152(2.5), 151(2.0), 150(1.7), 139(5.6), 115(3.1), 89(2.9); Mol. Weight Calcd for $C_{14}H_{11}N$: 193.0891. Found: 193.0891.

9-Azidophenanthrene **6.** 9-Bromo-10-azido-9, 10-dihydrophenanthrene (240 mg, 0.8 mmol) is stirred in pentane (6 ml) over silica gel (2.4 g, Merck 7733) at 25° for 6 hr. Silica gel is filtered off and the residue purified by plc SiO_2 eluted with pentane, the product with R_f 0.41 was scratched off, extracted with ether leading after removal of the solvent to 125 mg (71% yield) of 9-azidophenanthrene mp 115-116°. IR (KBr) 2120(s), 1390, 1310, 1265 cm^{-1}; ^{1}NMR ($CDCl_3$) δ 7.36 (s, 1H), 7.40-7.80, 8.00–820, 840–880 (3m, 8H); UV λ_{max} (ϵ) ($CHCl_3$) 246 shoulder (s) (34480), 256(s) (38620), 262 (40690), 272(s) (25520), 279(s) (17240), 298(s) (11380), 310(12760), 318 nm(s) (10690); MS(70eV) *m/e* 219 (M^+), 192, 191, 190, 189, 188, 187, 166, 165, 164, 163, 162, 152, 151, 150; Mol. Weight Calcd for $C_{14}H_9N_3$: 193.0796. Found: 193.0795.

9-Aminophenanthrene **7.** 9-azidophenanthrene (219 mg, 1 mmol) in anhyd ether (8 ml) is dropwise added to a stirred suspension of $AlLiH_4$ (42 mg, 1.1 mmol) in anhyd ether (1 ml) maintained at −15°. After stirring for 1.5 hr more, KOH aq (20%, 1 ml) is slowly added followed by celite (1 ml). The resulting suspension is filtered, extracted with ether and the organic layer dried over $MgSO_4$. The solvent is removed and the solide residue purified by plc (SiO_2, pentane/ether : 3/7) leading to 9-aminophenanthrene (160 mg, 83% yield, mp 139°) identical to an authentic sample (Aldrich 14, 910-1).

N-(3-Oxobutyl)-9,10-iminophenanthrene **8.** Freshly distilled methyl vinyl ketone (77 mg, 1.1 mmol) in anhyd THF (1.5 ml) is added to a stirred soln of 9,10-iminophenanthrene (193 mg, 1.0 mmol) in the same solvent (4 ml) at −15°. Triethylamine (two drops) are then added and stirring continued for a further 1.5 hr at this temp then at 25° for 40 hr. The solvent is removed *in vacuo* and the residue purified on plc (Al_2O_3, ether) leading to 210 mg of the desired alkylated imine (R_f 0.32) which is contaminated by unidentified impurities. Recrystallization from $CHCl_3$/ether/pentane, leads to pure **8** (mp 82-3°) in 60% yield. IR ($CHCl_3$) 3050, 3000, 2930, 2850, 1712, 1490, 1455, 1370 cm^{-1}; ^1H NMR ($CDCl_3$) δ 2.08 (s, 3H), 2.80 (m, 4H), 3.16 (s, 2H), 7.20–7.70 (m, 6H), 7.90-8.20 ppm (m, 2H); UV λ_{max} (ϵ) ($CHCl_3$) 240 (7690), 272 shoulder (s) (19040), 278 (20577), 293(s) (11920), 305 nm (5000); MS (70eV) *m/e* 263 (M^+), 206, 204, 193, 192 (M^+-C_4H_7O), 190, 179, 178 (M^+-C_4H_7NO), 177, 176, 166, 165, 164, 163, 152, 151, 150; Mol. Weight Calcd for $C_{18}H_{17}NO$: 263.1310. Found: 263.1309; Anal. calcd for $C_{18}H_{17}NO$: C, 82.10; H, 6.51. Found: C, 81.87; H, 6.62.

N-(3-Hydroxybutyl)-9,10-iminophenanthrene **9.** The ketone **8** (70 mg; 0.26 mmol) in anhyd THF (1 ml) is added at 0° to a stirred suspension of $AlLiH_4$ (24 mg, 0.62 mmol) in the same solvent (0.5 ml), a green colour appears. After stirring for 0.2 hr, the resulting suspension is hydrolysed with KOH aq (10%, 0.5 ml), filtered on a celite pad and the aqueous layer extracted with CH_2Cl_2. The organic layer is dried over $MgSO_4$, and the solvents removed. The solid residue is purified by plc (Al_2O_3, $CHCl_3$, R_f 0.75) and further recrystallized from $CHCl_3$/ether/pentane leading to the alcohol **9**, mp 110°, in 80% overall yield. IR($CHCl_3$) 3330, 2930, 2840, 1490, 1455, 1375 cm^{-1}; ^1H NMR ($CDCl_3$) 0.98-1.10 [m, 4H; 1.12 (d, J = 6Hz)], 1.64-1.88 (m, 2H), 2.40-2.76 (m, 1H), 2.76-3.32 [m, 3h; 3.08(s, 2H)], 3.80-4.04(m, 1H), 7.24-7.90, 8.00–8.20 ppm (2m, 8h); UV λ_{max} (ϵ) ($CHCl_3$) 242 (7890), 272 shoulder (s) (14490), 278 (15140), 293(s) (8070); 305 nm (3580). MS(70eV) *m/e* 165 (M^+), 207, 206, 204, 194, 193, 192 (M^+–C_4H_9O), 179,178 (M^+–C_4H_9NO), 177, 176, 166, 165, 164, 163, 152, 151, 150. Mol. Weight Calcd for $C_{18}H_{19}NO$: 265.1466. Found: 265.1455; Anal. Calcd for $C_{18}H_{19}NO$: C, 81.47; H, 7.22. Found: C, 81.42; H, 7.35.

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