Cyclic Amidines Part 25.[1] Intramolecular Cyclodehalogenation of Diazabenz[*a*]anthracenes and Diazabenzo[*c*]phenanthrenes

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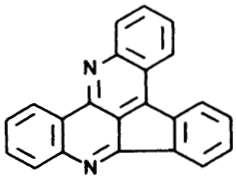
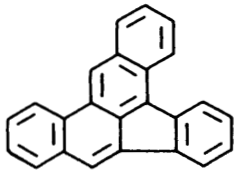
A previously unrecorded intramolecular cyclization which occurred during the palladium-catalysed hydrogenolysis of suitably disposed dichloroheterocycles [*e.g.* 7-chloro-6-(2-chlorophenyl)-5,12-diazabenz[*a*]anthracene (**3**) to 9,14-diazadibenz[*a,e*]aceanthrylene (**1**) and 6-chloro-7-(2-chlorophenyl)-5,8-diazabenzo[*c*]phenanthrene (**9**) to 9,14-diazadibenz[*a,e*]acephenanthrylene (**13**)] is reported.

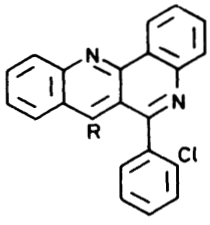
As a continuing part of our programme of investigating the relationship between the structure and carcinogenic activity of the intercalative tricycloquinazolines, it was decided to prepare the diazadibenz[*a,e*]aceanthrylene[2] (**1**) for mutagenic screening.



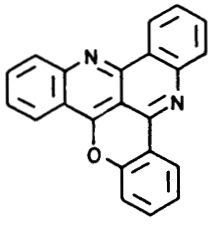
(**1**)



(**2**)



(**3**) R = Cl
(**4**) R = H



(**5**)

This compound is isosteric with the carcinogenic carbocyclic dibenzaceanthrylene (**2**) previously incorrectly assigned as dibenzo[*b,e*]pyrene,[3] and appeared readily accessible from the dichlorodiazabenzanthracene[4] (**3**). Indeed, a distillation of compound (**3**) from zinc dust produced the aceanthrylene (**1**) (6%) but contaminated with the intensely carcinogenic oxadiazatribenzophenalene (**5**) a by-product formed in a manner resembling those reactions previously reorted[4] for compound (**3**). Other direct methods (zinc in biphenyl, or magnesium or sodium amalgam in xylene) were not successful.

Vingiello[5] has shown that compound (**2**) can be prepared by a potassium hydroxide-induced dehydrohalogenation of 6-chloro-7-phenylbenz[*a*]anthracene so another route to the aceanthrylene (**1**) was available from the monochlorobenzanthracene (**4**). Compound (**4**) was itself accessible from a palladium-catalysed selective hydrogenolysis of the dichlorobenzanthracene (**3**) since the halogen in the heterocyclic ring in compound (**3**) is the more labile under such conditions.[6]

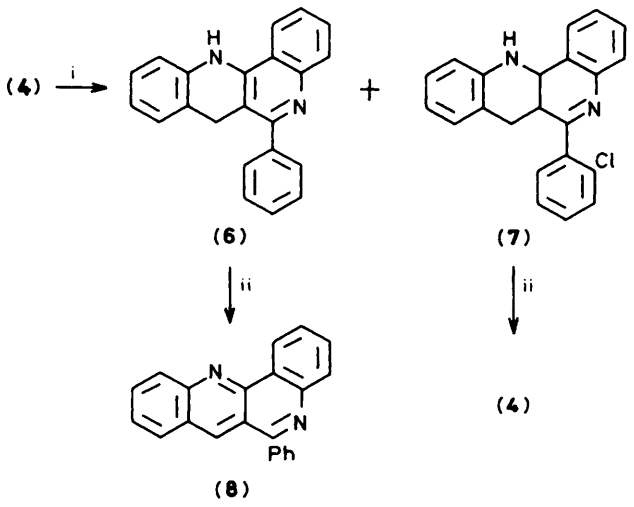
Using ethanol containing an equimolar quantity of potassium hydroxide as the solvent, the hydrogenation of compound (**3**) was stopped after the absorption of 1 mol equivalent of hydrogen. On air being allowed into the hydrogenator the final deep-red hydrogenated suspension turned yellow immediately and deposited a solid. The monochlorobenzanthracene (**4**) was isolated from the filtrate by chromatography on an alumina column and cyclized, using potassium hydroxide in biphenyl, to the required 9,14-diazadibenz[*a,e*]aceanthrylene (**1**).

The precipitated solid that was removed from the suspension at the end of the catalytic hydrogenation was then shown to be, unexpectedly, the same aceanthrylene (**1**). It had arisen from a cyclodehalogenation reaction which competed with normal hydrogenolysis. The red colour produced during the reaction was attributed to an easily reoxidized dihydro derivative of compound (**1**), because a separate hydrogenation of the pure aceanthrylene showed a rapid uptake of hydrogen (1.0 mol), and gave a deep red suspension which, on exposure to air immediately paled to yellow and deposited starting material in almost quantitative yield.

Intermolecular dimerization during hydrogenolysis over palladium has been reported. Busch[7] first recorded the production of biphenyl (40%) during the reduction of bromobenzene over palladium on $CaCO_3$ in alcohol containing an equivalent of strong base to prevent catalyst inhibition. Mayo and Hurwitz[8] extended and quantified this work showing that methanol was the only successful solvent, a finding not supported by our work. Busch[9] later reported the formation of 3,3′-bipyridyl from 3-bromopyridine and Albert[10] obtained 15% of 9,9′-biacridinyl from 9-chloroacridine. The only product from the hydrogenolysis of 4-chlorocinnoline was the 4,4′-dimer.[11] However intramolecular C–C bond formation under these conditions has not been recorded previously and this reaction was further examined.

The quantitative hydrogenation of the monochlorobenzanthracene (**4**) summarized in Scheme 1, was carried out. When the hydrogenation was stopped before completion a mixture of two closely related (t.l.c.) compounds was obtained. One of these products containing no halogen was present if the reaction was allowed to finish and required 2 mol equivalents of hydrogen. When the catalyst was removed and the solution concentrated, a high yield of the dihydrobenzanthracene (**6**) was obtained. Its structure was confirmed by physical evidence and by its oxidation, in high yield, to 6-phenyl-5,12-diazabenz[*a*]anthracene (**8**). The other component in the partially hydrogenated mixture was shown to be 7,12-dihydro-6-(2-chlorophenyl)-5,12-diazabenz[*a*]anthracene (**7**) since its oxidation gave back the starting material (**4**). Importantly, no trace of aceanthrylene (**1**) was detected in any of these reductions involving the monochlorobenzanthracenes, indicating that both halogen atoms need to be present and possibly undergo hydrogenolysis at the same active site on the catalyst for ring closure to occur.

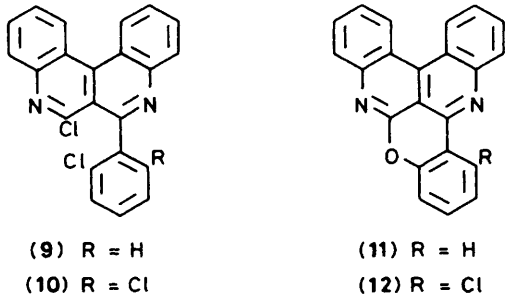
A second model chosen to examine the scope of this reaction



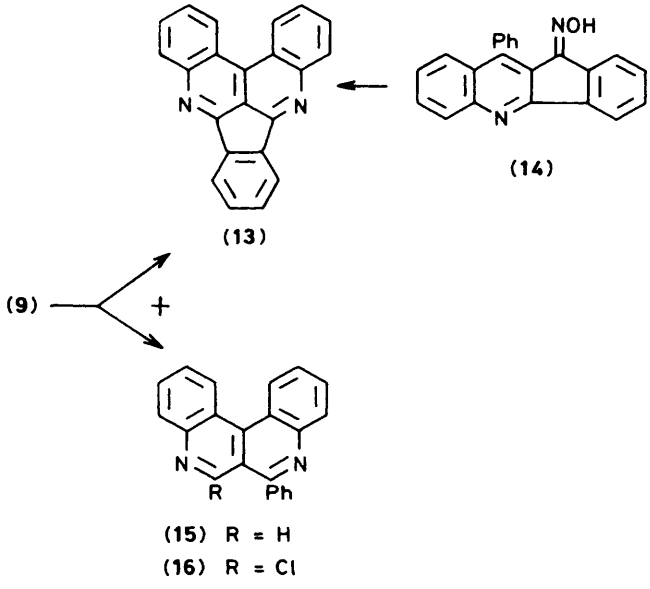
Scheme 1. *Reagents:* i, Pd–H_2; ii, $KMnO_4$

was 6-chloro-7-(2-chlorophenyl)-5,8-diazabenzo[*c*]phenanthrene (**9**), a compound related to the tricycloquinazolines in its biological ability to produce tumours.[12] It was available from the corresponding 6-hydroxybenzophenanthrene (**18**) obtained from a double Friedlander condensation of ethyl 2-chlorobenzoylacetate and 2,2′-diaminobenzophenone and its identity was confirmed when it was converted with sodium hydroxide in dimethylformamide into the oxadiazanaphthonaphthacene (**11**) and compared with an authentic sample.[12] The hydrogenation of compound (**9**), carried out under similar conditions, was not complicated by dihydro intermediates and after chromatography on alumina demonstrated again two competing modes of reduction (see Scheme 2).

The diazadibenzacephenanthrylene (**13**) (16%) was identified by comparison of its properties with those of an authentic sample derived either by the method of Partridge,[12] or from the polyphosphoric acid-induced cyclization of the oxime (**14**) of azabenzofluorenone. The normal hydrogenolysis product (**15**)



was shown to be the same as that derived from the hydrogenation of 7-chloro-6-phenyldiazabenzo[*c*]phenanthrene (**16**). In this last reaction, reduction of the monochloro compound (**16**) again showed no evidence of atypical cyclization to



Scheme 2.

Table 1. Summary of hydrogenations carried out

Compd.	Product	% Yield	M.p. (solvent)	Literature m.p. or analysis
(3)	(4)	45	222—224 °C (ethanol)	Found: C, 77.3; H, 3.9; N, 8.5 ($C_{22}H_{13}ClN_2$ requires: C, 77.6; H, 3.8; N, 8.2%)
	(1)	15	305—306 °C (toluene)	Found: C, 86.4; H, 4.2; N, 9.2 ($C_{22}H_{12}N_2$ requires C, 86.8; H, 4.0; N, 9.2%) $\lambda_{max.}$ (cyclohexane) 429, 408, 388, 367, 300, 288, 279, 257, 249, and 233 nm (log ε 3.80, 4.11, 4.11, 3.89, 4.0, 4.63, 4.61, 4.59, 4.62, and 4.57)
(4)	(6)	89[a]	275—280 °C[b] (toluene)	Found: C, 85.4; H, 5.1; N, 9.0 ($C_{22}H_{16}N_2$ requires: C, 85.7; H, 5.2; N, 9.1%)
(9)	(13)	16	270—271 °C (toluene)	270—271 °C[12]
	(15)	48	191—192 °C (toluene)	Found: C, 86.1; H, 4.3; N, 9.0 ($C_{22}H_{14}N_2$ requires: C, 86.3; H, 4.6; N, 9.2%)
(10)	(13) (15)	34, 44 resp.	as for (9)	
(12)	(11)	79	238—239 °C (xylene)	238—240 °C[12]
(16)	(15)	84	190—192 °C (light petroleum b.p. 100—120 °C)	as for compounds (9) and (15) above

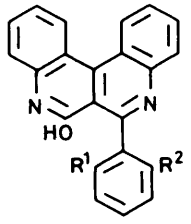
[a] From direct crystallization of reaction residue. [b] Oil bath at 250 °C on immersion of sample.

Table 2. Preparation of 6-substituted 7-aryldiazabenzophenanthrenes from 2,2′-diaminobenzophenone

Compd.	Reactant used reaction time, temperature, % yield	M.p. (solvent of crystallization	Analysis (C,H,N)
(17)	Ethyl benzoylacetate 20 min, 160 °C, 93	378—380 °C (D.M.F.)	Found: C, 82.1; H, 4.6; N, 8.2. ($C_{22}H_{14}N_2O$ requires: C, 82.0; H, 4.4; N, 8.6%)
(16)	(17) and thionyl chloride	197—198 °C (toluene–light petroleum)	Found: C, 77.6; H, 3.9; N, 7.9. ($C_{22}H_{13}ClN_2$ requires: C, 77.5; H, 3.9; N, 8.2%)
(18)	Ethyl 2-chlorobenzoylacetate, 90 min, 160 °C, 65	324—326 °C (D.M.F.)	Found: C, 73.9; H, 3.9; N, 7.6. $C_{22}H_{13}ClN_2O$ requires: C, 74.1; H, 3.7; N, 7.9%)
(9)	(18) and thionyl chloride 2 h, reflux, 75	218—220 °C (toluene)	Found: C, 70.1; H, 3.0; N, 7.8. ($C_{22}H_{12}Cl_2N_2$ requires: C, 70.4; H, 3.2; N, 7.5%)
(19)	Ethyl 2,6-dichlorobenzoylacetate, 4 h, 160 °C, 28	344—345 °C (decomp.) (2-ethoxyethanol)	Found: C, 67.8; H, 3.4; N, 6.8. ($C_{22}H_{12}Cl_2N_2O$ requires: C, 67.5; H, 3.1; N, 7.1%)
(10)	(19) and thionyl chloride 4 h, reflux, 46	232—234 °C (light petroleum, b.p. 100—120 °C)	Found: C, 65.0; H, 3.0; N, 6.6. ($C_{22}H_{11}Cl_3N_2$ requires: C, 64.6; H, 2.7; N, 6.8%)

compound (**13**), confirming the need for both halogens to be present, close to the same reactive catalyst centre.

Since it is likely that compound (**9**) exists predominantly as a conformer in which the halogen in the aromatic substituent will lie away from that in the heterocyclic ring, the trichloro derivative (**10**) was prepared in order to increase the proportion of suitably disposed conformers. Compound (**10**) was, therefore, prepared in a similar way to compound (**9**) from (**19**) although



(**17**) $R^1 = R^2 = H$
(**18**) $R^1 = H$; $R^2 = Cl$
(**19**) $R^1 = R^2 = Cl$

more forcing conditions were needed. This too was converted to compounds (**12**) and (**11**) for confirmation of its structure and then hydrogenated. Only compounds (**13**) and (**15**) were present after reduction but the yield of the cyclized acephenanthrylene (**13**) rose to 37%, more than double that derived from the dichloro precursor (**9**).

Experimental

M.p.s were recorded on a Gallenkamp apparatus and are uncorrected, column chromatography was carried out using activated neutral alumina supplied by Woelm and u.v. spectra determined using a Perkin-Elmer spectrophotometer PE55OS.

6-(2-*Chlorophenyl*)-5,12-*diazabenz*[a]*anthracene* (**4**).—A stirred suspension of potassium hydroxide (0.6 g), and palladium catalyst (10% Pd-on-charcoal, 0.5 g) in ethanol (50 ml) was allowed to equilibrate with hydrogen at atmospheric pressure. A solution of 7-chloro-6-(2-chlorophenyl)-5,12-diazabenz[*a*]anthracene[4] (1.0 g) in toluene (50 ml) was introduced and hydrogenation continued until 1.1 mol equivalents of hydrogen had been absorbed. After removal of precipitated 9,14-diazadibenz[*a,e*]aceanthrylene (0.12 g) and solvent, the residue was chromatographed on an alumina column, eluting with toluene and the fractions up to but not including an intensely green fluorescent band, were collected and evaporated. Crystallization of the residue from ethanol, gave 6-(2-*chlorophenyl*)-5,12-*diazabenz*[a]*anthracene* (**4**) as colourless plates (0.4 g, 45%), m.p. 222—224 °C (Found: C, 77.3; H, 3.9; N, 8.5. $C_{22}H_{13}ClN_2$ requires C, 77.6; H, 3.8; N, 8.2%); $\lambda_{max.}$(EtOH) 356, 340, 280, and 246 nm (log ε 3.95, 3.88, 4.86, and 4.43).

The hydrogenation of other compounds in this report were carried out in a similar manner to that described above and relevant data are recorded in Table 1.

9,14-*Diazadibenz*[a,e]*aceanthrylene* (**1**).—6-(2-Chlorophenyl)-5,12-diazabenz[*a*]anthracene (0.25 g) and fused, powdered potassium hydroxide (0.5 g) were refluxed together for 6 h in biphenyl (5 g), extracted into benzene, placed on an alumina column and washed free of biphenyl [light petroleum (b.p. 80—100 °C)]. Development with toluene gave an intensely green fraction which deposited 9,14-*diazadibenz*[a,e]*aceanthrylene* (0.045 g, 20%), as yellow needles, m.p. 305—306 °C (Found: C, 86.4; H, 4.2; N, 9.2. $C_{22}H_{12}N_2$ requires C, 86.8; H, 4.0; N, 9.2%).

The corresponding *picrate*, crystallized from toluene as dark red needles, m.p. 270—273 °C (Found: C, 63.5; H, 2.9; N, 12.9. $C_{28}H_{15}N_5O_7$ requires C, 63.1; H, 2.8; N, 13.1%).

6-*Phenyl*-5,12-*diazabenz*[a]*anthracene* (**8**).—The solid, obtained by heating a suspension of 7,12-dihydro-6-phenyl-5,12-diazabenz[*a*]anthracene (0.1 g) in a solution of sodium dichromate (0.5 g) and sulphuric acid (2M; 5 ml) under reflux for 30 min and basification, gave on crystallization from ethanol, 6-*phenyl*-5,12-*diazabenz*[a]*anthracene* as colourless needles (0.8 g, 80%), m.p. 207—208 °C (Found: C, 85.8; H, 4.4; N, 8.9. $C_{22}H_{14}N_2$ requires C, 86.3; H, 4.6; N, 9.2%); $\lambda_{max.}$(EtOH) 359, 342s, 280, 246, and 220 nm (log ε 3.96, 3.87, 4.83, 4.50, and 4.62).

The corresponding *picrate* melted at 263—265 °C (decomp.) after crystallization from toluene (Found: C, 62.4; H, 3.0; N, 13.4. $C_{28}H_{17}N_5O_7$ requires C, 62.8; H, 3.2; N, 13.1%).

6-*Hydroxy*-7-*phenyl*-5,8-*diazabenzo*[c]*phenanthrene* (**17**).—Addition of methanol (5 ml) to the glass obtained from heating 2,2′-diaminobenzophenone[12] (1.8 g) and ethyl benzoylacetate (2 g) with acetic acid (0.3 ml) at 160 °C for 20 min gave 6-*hydroxy*-7-*phenyl*-5,8-*diazabenzo*[c]*phenanthrene* (2.55 g, 93%),

m.p. 377—378 °C raised to 378—380 °C on crystallization from dimethylformamide (yellow prisms).

6-Chloro-7-phenyl-5,8-diazabenzo[c]*phenanthrene* (**16**).—The foregoing 6-hydroxyphenanthrene (1.6 g) was heated under reflux in freshly distilled thionyl chloride (20 ml) containing dimethylformamide (2 ml) for 2 h. After this the excess of solvent was distilled off and the mixture poured onto ice (20 g) containing sodium hydroxide (10 ml; 2M) to give a residue which when chromatographed on alumina (toluene) afforded the *6-chloro derivative* (1.4 g, 83%), m.p. 197—198 °C.

The 6,7-disubstituted 5,8-diazabenzo[*c*]phenanthrenes shown in Table 2 were prepared in a manner similar to that described for the preparation of 6-hydroxy-7-phenyl-5,8-diazabenzo[*c*]phenanthrene and the corresponding 6-chloro derivative.

Ethyl 2-Chlorobenzoylacetate.—This was prepared by the method of Thorp *et al.*[13]

Ethyl 2,6-Dichlorobenzoylacetate.—A stirred mixture of diethyl carbonate (70 ml) and 2,6-dichloroacetophenone[14] in an oil-bath at 140—150 °C was treated with a solution of sodium (1.22 g) in anhydrous ethanol (30 ml) at a rate sufficient to maintain a slow distillation of ethanol. When no more ethanol distilled, the reaction mixture was poured into aqueous hydrochloric acid (2M; 250 ml), and the organic layer removed and fractionated to give *ethyl 2,6-dichlorobenzoylacetate* (8.2 g, 60%), as a colourless oil, b.p. 132—134 °C/0.6 mmHg (Found: C, 50.5; H, 4.0. $C_{11}H_{10}Cl_2O_3$ requires C, 50.6; H, 3.9%).

10-Oxa-9,15-diazanaphtho[1,2,3-fg]*naphthacene* (**11**).—This compound (0.056 g, 62%) was obtained after chromatographic purification of the solid derived from heating a solution of dimethylformamide (2 ml) and sodium hydroxide (2M; 0.25ml) containing 6-(2-chlorophenyl)-7-hydroxy-5,8-diazabenzo[*c*]-phenanthrene (0.1 g). It melted at 237—239 °C and did not depress the m.p. of an authentic sample.[12] The *14-chloro-naphthonaphthacene* (**12**) (72%) was obtained in a similar way from the trichlorophenanthrene (**10**) as colourless prisms, m.p. 229—230 °C (toluene) (Found: C, 74.3; H, 3.2; N, 7.6. $C_{22}H_{11}ClN_2O$ requires C, 74.5; H, 3.1; N, 7.9%).

11-Oxo-10-phenyl-1H-benzo[b]*carbazole*.—Indan-1,3-dione (4.38 g) and 2-aminobenzophenone (5.91 g) were heated together at 160 °C for 60 min with acetic acid (1 ml), stirred with methanol (30 ml) and gave the *benzocarbazole* (6.3 g, 94%), m.p. 188—189 °C after crystallization from toluene (Found: C, 85.9; H, 4.4; N, 4.2. $C_{22}H_{13}NO$ requires C, 86.0; H, 4.3; N, 4.5%).

The *oxime* (**14**) of this ketone was prepared (93%) and existed as colourless prisms, m.p. 288—290 °C (decomp.) (from xylene) (Found: C, 81.8; H, 4.7; N, 8.4. $C_{22}H_{14}N_2O$ requires C, 82.0; H, 4.4; N, 8.7%). This same oxime could be prepared by treating 2-aminobenzophenone with the *mono-oxime* of indan-1,3-dione, m.p. 231—233 °C (Found: C, 67.4; H, 4.0; N, 8.5. $C_9H_7NO_2$ requires C, 67.1; H, 4.3; N, 8.7%).

9,14-Diazadibenz[a,e]*acephenanthrylene* (**13**).—This compound was obtained (2.25 g, 91%) by crystallizing from dimethylformamide, the solid obtained when 11-hydroxyimino-10-phenyl-1*H*-benzo[*b*]carbazole (3 g) was heated to 170 °C with polyphosphoric acid (40 g) for 15 min; it formed colourless prisms, m.p. and mixed m.p. 270—272 °C.[12]

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Received 25*th May* 1985; *Paper* 5/886