The Synthesis and Characterisation of Some 2,7-Diazaphenanthrene Derivatives

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2,7-Diazaphenanthrene was synthesised in moderate yield by the modified Pomeranz-Fritsch reaction by condensing diethoxyethanal with 1,4-benzenebismethanamine, followed by ring closure with 20% oleum, and its spectral characteristics recorded. A similar reaction with diethyl 1,4-benzenebis(3-aminopropanoate) gave either 2,7-diaza-1,8-dimethylphenanthrene or 2,7-diaza-1,8-phenanthrenebis(methylsulphonic acid), depending on the conditions of the ring closure reaction. The bis methiodides of these compounds were tested for phospholipase A_2 inhibitory action but were found to be inactive.

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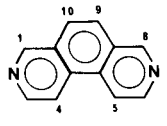
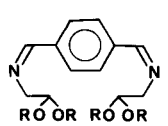
The synthesis of some substituted 2,7-diazaphenanthrenes was undertaken in order to test the possibility that they might intercalate with suitably oriented tyrosine side chains of phospholipase A_2. In 1940 Ruggli and Schetty [1] described the synthesis of 2,7-diazaphenanthrene, **1**, but this ring system appears to have attracted no further attention. They reported that a conventional Pomeranz-Fritsch synthesis failed but that if the imine **2** was first reduced and then treated with oleum then **1** was obtained in low yield. They describe this as a crystalline compound, mp 225°, unstable in air, exhibiting a blue fluorescence in solution; the bis methiodide had the correct elemental composition but no further proof of structure was given and the compound was not investigated further.

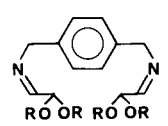
Schlittler and Müller's variation [2] of the Pomeranz-Fritsch reaction, using diethoxyethanal with a substituted benzylamine instead of diethoxyethylamine with an aromatic aldehyde, often gives greatly improved yields, and this was found to be true in this case. Treatment of the imine **3** with 20% oleum at room temperature gave, in moderate yield, a compound mp 146-147°, markedly different from that reported by Ruggli and Schetty, but which we identify as 2,7-diazaphenanthrene, **1**. Hot concentrated sulphuric acid as the condensing agent gave trace amount of **1**; with oleum at low temperatures, and with other Lewis acids the reaction failed completely.



1.



2. R = C_2H_5



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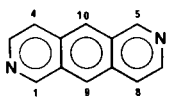

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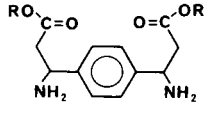
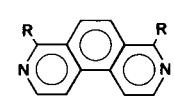


5. R = C_2H_5



6. R = CH_3

7. R = CH_2SO_2OH

The compound had an elemental composition and mass spectrum (molecular ion m/e 180) corresponding to **1**; it was stable in air, was intensely fluorescent in solution and had a uv spectrum characteristic of a condensed aromatic system. In principle the second ring closure could lead to the linear diazaanthracene **4**, although it is well known that the non-linear aromatic systems are the more stable. The compound gave a single peak on glc and ran as a single component on tlc and high voltage paper electrophoresis; its nmr spectrum integrated cleanly to the required number of protons, with no sign of minor components, all of which suggested that it was a single substance. 2,6-Diazaanthracene (**4**) and 2,7-diazaphenanthrene (**1**) can be distinguished by their nmr spectra. Inspection of the chemical shifts for the protons in naphthalene, isoquinoline, phenanthrene and anthracene suggested that the protons at C-9 and C-10 of **4** should exhibit a singlet at δ 8.3 whereas the protons at C-9 and C-10 of **1** should be a singlet at a lower frequency, δ 7.7, the spectra for the other protons being similar for **1** and **4**. A singlet at δ 7.8 was observed, confirming the identity of the product as 2,7-diazaphenanthrene. The ultra-violet spectrum was found to be *p*H dependent due to protonation of the ring nitrogen atoms. Between *p*H 6.0 and 3.5 a new band appeared at 375 nm; and between *p*H 3.5 and 1.0 this band moved to 383 nm. On this basis the pK_as of the di- and mono-protonated conjugate acids are estimated as 2.5 and 4.5.

Our studies of potential enzyme inhibitors required diazaphenanthrenes substituted with acidic functional groups, and so the reaction was repeated with the bis-β-amino acid ester **5**. Ring closure of the derived imine required a higher temperature, which resulted in the loss of the ethoxycarbonyl group, the product of the reaction depending on the conditions employed. When treated with 20% oleum at 60° overnight the principle product was 2,7-diaza-1,8-dimethylphenanthrene (**6**) very similar in its properties to the parent compound. When the reaction was carried out in excess oleum at 50° substantial quantities of

an alkali soluble compound were obtained which was isolated as the sparingly soluble bis methylene sulphonic acid **7**. The nmr (in deuterium oxide) of the soluble sodium salt showed six aromatic and four aliphatic protons, though the latter were very close to the water peak and were difficult to integrate. Since the methylene groups had not been lost, and all the aromatic protons were present (two doublets and a singlet, 2:2:2, as expected) the sulphonate groups could not be attached to the ring. The carbanion resulting from decarboxylation could react with the sulphur trioxide in the reaction medium to give a sulphonic acid. At higher reaction temperatures this step would be reversible and the carbanion can take the more difficult, but irreversible step of abstracting a proton from sulphuric acid to give the dimethyl compound.

Shifrin [3] has shown that quaternary pyridinium salts (*e.g. N*-methylnicotinic acid derivatives) can form charge transfer complexes with phenols. The bis methiodides of compounds **1**, **6** and **7** were therefore prepared in the hope that they might form such complexes with tyrosine residues near the active site of phospholipase A_2, [4]. When a solution of the bis methiodide of **1** was treated with the disodium salt of 4,4′-dihydroxybiphenyl a very broad, low intensity absorption band was produced, extending out to 800 nm, indicating some charge transfer complex formation. However none of these compounds showed any significant inhibitory action against the enzyme phospholipase, although this enzyme contains two tyrosine residues that might adopt an antiparallel conformation and hence form an intercalation complex.

EXPERIMENTAL

Melting points are uncorrected. Microanalyses were performed by Dr. F. B. Strauss, Oxford. Infra-red spectra were recorded on a Perkin Elmer 298 spectrophotometer, uv spectra using a Varian Superscan 3 and pmr spectra using a Hitachi Perkin Elmer R 24B. Mass spectra were determined by Dr. D. J. Harvey, using a V. G. Micromass 12B, accelerating voltage 2.5 Kv, electron energy 25 ev, source temperature 230°.

1,4-Benzenebis-*N*-(2,2-diethoxyethylidene)methanamine (**3**).

1,4-Benzenebis(methanamine) (2.57 g, 0.019 mole), diethoxyethanal (5.2 g, 0.04 mole) and benzene (20 ml) were refluxed in a Dean and Stark apparatus for 15 minutes. The mixture was allowed to cool, then filtered to remove a small quantity of yellow solid. The filtrate was evaporated to an orange oil, and this was dried at over 150° under 1 mm Hg pressure for an hour, yield 6.5 g, 94% n_D^{18}: 1.511; ir: ν 1670 (-C=N), 1060 (-O-C-O-) cm^{-1}.

2,7-Diazaphenanthrene (**1**).

Oleum (20%, SO_3, 25 ml) was cooled in an ice bath, and 1,4-benzenebis *N*-(2,2-diethoxyethylidene)methanamine (5.0 g, 0.014 mole) added dropwise with stirring over 30 minutes, keeping the temperature at 15-20°. The mixture then stood at room temperature overnight.

The mixture was poured into ice (400 g) and the solution neutralised with solid sodium carbonate, and basified with sodium hydroxide (2 *M*, 50 ml). The solution was filtered, the residue washed with ether (100 ml), and the filtrate extracted with ether (2 × 100 ml). The ether layers were combined, dried over magnesium sulphate, and evaporated to give a yellow solid, 0.74 g, 30%. The crude product was recrystallised from 60/80 petrol/toluene (1:1), the hot solution being decanted from some brown oil, mp 146-147°; uv (ethanol): λ max (log ε) 234 (s) (4.75), 239 (4.80), 267 (4.04), 277 (4.18), 288 (4.20), 312 (s) (3.0), 325 (3.38), 340 (3.67), 357 (3.73); fluorescence (ethanol); λ max emmission, 380 nm; λ max absorption 290 nm; pmr (carbon tetrachloride): δ 7.8 (s, H-9, 10, 2H), 8.2 (d, H-4, 5, 2H), 8.65 (d, H-3, 6, 2H), 9.1 (s, H-1, 8, 2H); ms: 180 (M^+, 100), 153 (M-HCN, 23), 126 (M-2HCN, 7).

Anal. Calcd. for $C_{12}H_8N_2$: C, 79.98; H, 4.47; N, 15.55. Found: C, 79.57; H, 4.54; N, 15.66.

1,4-Benzenebis(3-aminopropanoic Acid) (**5**, R = H).

1,4-Benzenedicarboxaldehyde (44.7 g, 0.33 mole), malonic acid (69.7 g, 0.67 mole), ammonium acetate (77.0 g, 1.00 mole) and aqueous ethanol (80%, 160 ml) were stirred and heated on a mantle under reflux for 20 hours. The solid quickly dissolved, and slowly solid separated again. The mixture was filtered, and the solid washed with warm ethanol (200 ml), warm water (2 × 200 ml), then ethanol, ether and finally dried, 57.3 g, 70%. The uv spectrum of this material, λ max (0.1 *N* sodium hydroxide) 278, (apparent log ε 3.89), indicated contamination with the unsaturated mono deaminated product. This was most conveniently removed after esterification.

Diethyl 1,4-Benzenebis(3-aminopropanoate) Dihydrochloride (**5**).

Ethanol (280 ml) was stirred in a dry ice/trichoroethene bath while thionyl chloride (100 ml, 164 g, 1.38 moles) was added slowly keeping the temperature below 0°. The impure 1,4-benzenebis(3-aminopropanoic acid) (57.3 g, 0.23 mole) was added, and the mixture stirred as the temperature was raised slowly to 45° over 1 hour. The mixture was stirred for a further 2 hours at 45-50°, then at reflux for 2 hours. The reaction mixture was evaporated to dryness, ethanol was added (250 ml) and re-evaporated to dryness. The solid was dispersed into ethanol (200 ml) and refluxed for 10 minutes. Ether (100 ml) was added carefully down the condenser, and the mixture allowed to stand overnight. The precipitated solid was filtered, washed with ether/ethanol and was redissolved in aqueous ethanol (95%, 500 ml), filtered hot, and reprecipitated with ether (1 litre). When completely cool the solid was filtered off, washed with ether/ethanol (2:1, 300 ml) and dried in a vacuum dessicator, yield 40.2 g, 32% mp 200° dec; uv (water): λ max (log ε) 257 (2.51), 262 (2.56), 268 (2.44).

Anal. Calcd. for $C_{16}H_{26}Cl_2N_2O_4$: C, 50.30; H, 6.82; N, 7.35. Found: C, 49.81; H, 6.77; N, 7.35.

Diethyl 1,4-Benzenebis-3(2,2-diethoxyethylideneamino)propanoate.

Diethyl 1,4-benzenebis(3-aminopropanoate) dihydrochloride (46.9 g, 0.123 mole) was dissolved in water (124 ml) and the solution placed in a separating funnel with benzene (1.25 ℓ). Aqueous sodium hydroxide was added (10 *M*, 40 ml, 0.4 mole) and the mixture thoroughly shaken. The benzene layer was separated and excess water absorbed with magnesium sulphate. The filtered solution was added to diethoxyethanal (32.5 g, 0.245 mole) and the mixture distilled until the distillate was clear and contained no more water droplets. The residue was evaporated to an oil that solidified on standing. This was recrystallised from 60/80° petrol/benzene (99:1, 500 ml), yield 51.4 g, 78%, mp 96.9°.

Anal. Calcd. for $C_{28}H_{43}N_2O_8$: C, 62.69; H, 8.21; N, 5.22. Found: C, 62.83; H, 8.11; N, 5.41.

1,8-Dimethyl-2,7-diazaphenanthrene (**6**).

Diethyl 1,4-benzenebis-3(2,2-diethoxyethylideneamino)propanoate (3.0 g, 5.6 mmoles) was added portionwise to oleum (20% sulphur trioxide, 10 ml) while shaking and cooling in a cold water bath. The solid dissolved, and the mixture was kept at 60° overnight.

The mixture was poured into water (100 ml), and the solution boiled. A hot solution of barium hydroxide (65 g) in water (100 ml) was added, and the alkaline solution neutralised by passing carbon dioxide for several minutes. The precipitated barium salts were filtered from the hot solution. On cooling the filtrate, solid crystallised out, and this was filtered and dried, yield 0.25, 22%.

The solid was recrystallised from 60/80° petrol/benzene (2:1, 15 ml),

the hot solution being decanted from some brown oil, pale yellow crystals, 0.14 g, 12%, mp 185-188°; uv (ethanol): λ max (log ε) 218 (4.48), 241 (4.78), 276 (4.11), 287 (4.28), 326 (3.48), 341 (3.74), 358 (3.78); pmr (carbon tetrachloride): δ 2.9 (S, CH_3, 6H), 7.85 (S, H-9, 10, 2H), 8.0 (d, H-4, 5, 2H), 8.45 (d, H-3, 6, 2H); ms: 208 (M^+, 100), 207, 193 (M-CH_3, 4), 192 (4), 181 (M-HCN, 7), 180 (8).

Anal. Calcd. for $C_{14}H_{12}N_2$: C, 80.77; H, 5.77; N, 13.46. Found: C, 80.79; H, 5.77; N, 13.33.

2,7-Diaza-1,8-phenanthrenebis(methylsulphonic Acid) and Sodium Salt (7).

Diethyl 1,4-benzenebis-3-(2,2-diethoxyethylideneamino)propanoate (10.8 g, 0.02 mole) was added portionwise to oleum (20% sulphur trioxide, 80 ml) with stirring, while keeping the temperature below 45° by cooling in a water bath. The mixture was then stood in an oil bath at 50° overnight.

The mixture was poured into water (400 ml), and a hot aqueous solution of barium hydroxide (65% w/v) added until the solution was just alkaline (750 ml). Carbon dioxide was passed to restore neutrality, and the hot suspension filtered; the residue was washed with hot water (400 ml) and pressed dry. The filtrate and washings were cooled and passed down a cation exchange column (Amberlite I.R. 120 (H), 100 g), the last traces of product being washed off with deionized water. The solution was evaporated to about 400 ml, boiled, then allowed to cool. The solid was filtered, washed with water, ethanol then ether and allowed to dry, yield 2.0 g, 26%, mp 310°.

The sulphonic acid (1.9 g, 4.9 mmoles) was dissolved in aqueous sodium hydroxide (1.0 *M*, 12 ml, 12 mmoles) and centrifuged to remove some insoluble matter. Ethanol was added (60 ml), and the precipitated salt was filtered, washed with ethanol, ether then dried in a vacuum dessicator, yield 2.2 g (hygroscopic), 90%, mp 310°; pmr (deuterium oxide): δ 7.75 (d, H-3, 6, 2H), 7.5 (s, H-9, 10, 2H), 6.9 (d, H-4, 5, 2H), 4.4 (s, CH_2, 4H). A small portion of sodium salt was dissolved in water and dilute hydrochloric acid was added. The precipitated acid was filtered, washed and dried *in vacuo* at 50°.

Anal. Calcd. for $C_{14}H_{12}N_2S_2O_6 \cdot 0.5H_2O$: C, 44.56; H, 3.45; N, 7.43; S, 16.98. Found: C, 44.78; H, 3.61; N, 7.51; S, 16.95.

2,7-Dimethyl-2,7-diazoniaphenanthrene Diiodide.

2,7-Diazaphenanthrene (0.175 g, 0.97 mmole) was dissolved in DMF (20 ml) and iodomethane (1.2 ml, 2.7 g, 19 mmoles) added. The flask was fitted with an efficient condenser and stood in a water bath at 40° overnight. After cooling, the orange solid was filtered, washed with DMF, ethanol, then ether, and dried in a vacuum dessicator, yield 0.34, 75%, mp 274-278°; uv (water): λ max (log ε) 245 (4.83), 269 (4.11), 284 (4.02), 368 (3.72), 388 (3.79).

Anal. Calcd. for $C_{14}H_{14}I_2N_2$: C, 36.31; H, 3.20; N, 6.03. Found; C, 36.48; H, 3.45; N, 5.90.

2,7-Dimethyl-2,7-diazonia-1,8-phenanthrenebis methylsulphonate.

Disodium 2,7-diaza-1,8-phenanthrenebis methylsulphonate (0.5 g) was dissolved in DMF/water (3:1, 50 ml). Iodomethane was added (2 ml) and the mixture was allowed to stand in a water bath at 40° overnight. The cooled mixture was filtered, the solid was pressed dry, and recrystallised from DMF/water (1:1, 60 ml), and dried in a vacuum over at 50°, yield 0.25 g, 60%, mp 300°.

Anal. Calcd. for $C_{16}H_{16}N_2S_2O_6 \cdot H_2O$: C, 47.36; H, 4.35; N, 6.76; S, 15.46. Found: C, 47.09; H, 4.48; N, 6.85; S, 15.66.

Acknowledgements.

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[4] Observation based on crystallographic data on a bovine phospholipase A_2 supplied by Professor J. Drenth.