312. *Researches in the Phenanthridine Series. Part II. Nitro- and Amino-phenanthridines.*

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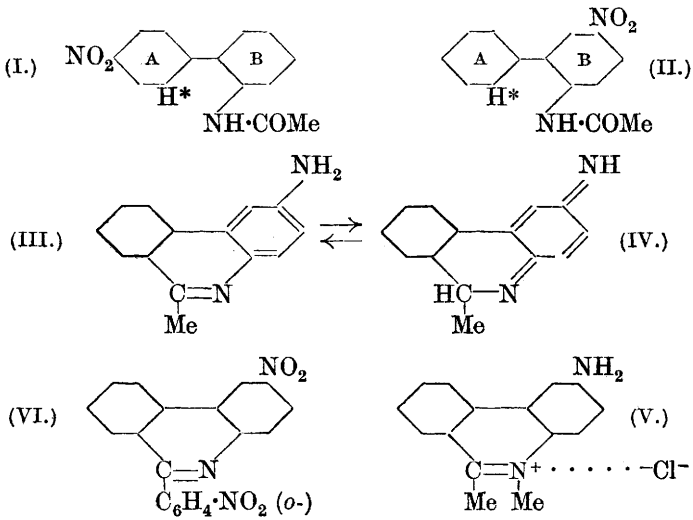
THE new synthesis of phenanthridine derivatives from acyl-*o*-xenylamines (J., 1931, 2447) has now been applied successfully to nuclear-substituted acet-*o*-xenylamides, two readily available compounds being 4′-nitro- and 5-nitro-2-acetamidodiphenyl (Scarborough and Waters, J., 1927, 89; Bell, J., 1928, 2773, respectively). Dehydration-condensation by means of phosphorus oxychloride has led to the corresponding nitro-9-methylphenanthridines, although the yield of 7-*nitro*-9-*methylphenanthridine* from (I) is very small compared with that of 3-*nitro*-9-*methylphenanthridine* from (II), a difference which may be attributed to polar influence of the nitro-group on the strategic hydrogen atom H*. Such a group in ring A



would depress the mobility of H*, whereas in ring B it would have only a slight effect. These results are compatible with the conclusions of Callow, Gulland, and R. D. Haworth (J., 1929, 1444), who state that "facile closure of the *iso*quinoline ring is dependent on the presence of a strongly *p*-directive group in the *p*-position to that at which condensation is to take place." The corresponding formyl compounds could not be converted into nitrophenanthridines by phosphorus oxychloride.

These nitromethylphenanthridines are well-defined crystalline substances possessing markedly basic properties. 3-Nitro-9-methyl-

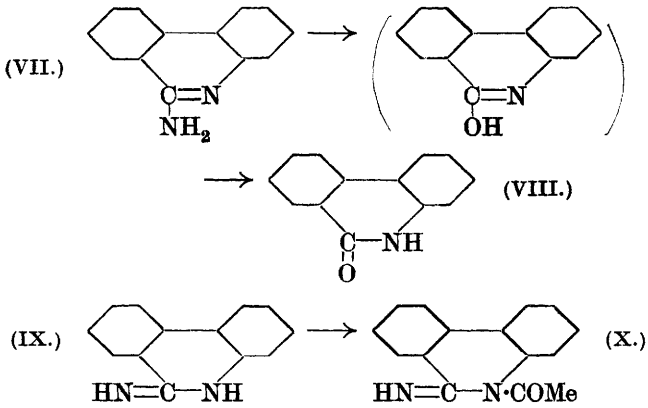
phenanthridine was reduced to the corresponding *amine*, a bright yellow substance which dissolves in dilute acid to an orange yellow solution, and yields a yellow *acetyl* compound. This amino-molecule contains the possibility of quinonoid tautomerism (III⇌IV). The less acidic character of 3-*amino*-9 : 10-*dimethylphenanthridinium chloride* (V) unfortunately did not confer on it the expected lower toxicity and greater therapeutic value than were presented by the 9-aminophenyl-10-methylphenanthridinium chlorides. To obtain closer analogy to the acridine antiseptics, an attempt was made to prepare a quaternary salt containing two free primary amino-groups. The interaction of 2-o-*nitrobenzamido*-5-*nitrodiphenyl* and phosphoryl chloride resulted in too small a yield of the non-basic 3-*nitro*-9-o-*nitrophenylphenanthridine* (VI) for further experiment.

In our previous communication it was mentioned that the new synthesis fails in the case of form-*o*-xenylamide, so that Pictet and Hubert's method of fusion with zinc chloride (*Ber.*, 1896, **29**, 1182) must be employed in the preparation of phenanthridine itself. This process has, however, been improved by removing *o*-xenylamine, the chief by-product, by acetylation, thereby avoiding tedious fractional crystallisations of mercurichlorides. The base has the unusual property of combining with 2 mols. of nitric acid to form a well-defined crystalline *dinitrate*, $C_{13}H_9N,2HNO_3,2H_2O$, converted into normal *nitrate* $C_{13}H_9N,HNO_3$ by water, alcohol, or acetone. Mononitration of the base occurred when this anhydrous nitrate was added to sulphuric acid, and three nitrophenanthridines were separated with difficulty from the complex product. Owing to small yield these isomerides were not investigated further.

In that phenanthridine is a dibenzopyridine, it appeared likely that the sodamide process (Tschitschibabin and Zeide, *J. Russ. Phys. Chem. Soc.*, 1914, **46**, 1216; *A.*, 1915, i, 590) would prove suitable for the preparation of 9-*aminophenanthridine*. Vigorous reaction occurred with sodamide, and a good yield of the amino-compound was obtained. Contrary to previous experience with pyridine derivatives, reaction had mainly subsided after 20 minutes although a slow evolution of hydrogen continued for several hours. An estimation of hydrogen always revealed a deficiency in the amount of this gas. Both anomalies are probably due to the affinity of phenanthridine and its derivatives for hydrogen and the instability of the dihydro-compounds : autoreduction would facilitate amination, but hydrogen would be lost subsequently. An almost quantitative yield of 9-aminophenanthridine results also from the interaction of a dimethylaniline solution of phenanthridine with ammonia in contact with sodium. This more favourable method depends mainly on dimethylaniline as solvent, for when

mesitylene is used the yield is greatly diminished. The amine was always accompanied by a small quantity of a brown crystalline base, the nature of which has not been elucidated.

9-Aminophenanthridine is a colourless crystalline solid soluble in dilute acids to colourless solutions; its *lactate* and *acetate*, the aqueous solutions of which are neutral, are under chemotherapeutic investigation. Diazotisation could not be accomplished in acid solution, or by the Bamberger–Rüst method (*Ber.*, 1900, **33**, 3511); the base reacts slowly with nitrous acid, yielding phenanthridone (VIII) as sole product. By acetylation one *monoacetyl* compound was obtained, soluble in dilute acid but hydrolysed thereby, even by dilute acetic acid. Another anomaly was revealed in that a quaternary salt was not obtained from it by the usual methods. These facts suggest that the tautomerism postulated by Tschitschibabin for α-aminopyridine may in this case be determined in one direction, so that the base may not be a true aminophenanthridine (VII) but an internal amidine (IX), yielding an *acetyl* compound of consitution (X) which did not yield a single product with one molecule of methyl sulphate.



An authentic specimen of phenanthridone was prepared in small yield by zinc chloride fusion of either o-*xenylcarbamide* or *methyl* o-*xenylcarbamate*, obtainable from oily *o*-xenylcarbimide prepared from *o*-xenylamine (Morgan and Pettet, J., 1931, 1124).

Experimental.

7-*Nitro*-9-*methylphenanthridine*.—4′-Nitro-2-acetamidodiphenyl reacted with $POCl_3$ alone, or more vigorously in admixture with PCl_5, with evolution of HCl. Evaporation of excess of reagent left a gum, which was extracted repeatedly with hot 5*N*-HCl. The *nitrophenanthridine*, a slight yellow ppt. liberated from this extract on neutralisation, crystallised from C_6H_6 in buff-coloured needles, m. p. 243—245° (Found, by micro-analysis: C, 70·55; H,

4·35; N, 11·2. $C_{14}H_{10}O_2N_2$ requires C, 70·6; H, 4·2; N, 11·75%). This nitro-compound and the following isomeride are essentially like other nitrophenanthridines in being more sol. in C_6H_6 than in EtOH.

3-*Nitro*-9-*methylphenanthridine*.—When 5-nitro-2-acetamidodiphenyl (16 g.) and $POCl_3$ (32 g.) were boiled, vigorous evolution of HCl occurred. After 2 hrs., excess of reagent was evaporated and the residual gum was extracted repeatedly with N-H_2SO_4 (about 500 c.c.). Neutralisation of the extract gave a yellow flocculent ppt. (12 g.; 80% yield) which crystallised from C_6H_6 in transparent, brown, elongated prisms, m. p. 201°. It dissolved readily in fairly dil. mineral acid, but was almost insol. in dil. HOAc (Found : C, 70·55; H, 4·75; N, 11·8%).

3-*Amino*-9-*methylphenanthridine*.—Reduction of the nitro-compound (10 g.) proceeded rapidly with Fe filings (10 g.) and hot acidulated H_2O. The black aggregate of amine and Fe_3O_4 was extracted (Soxhlet) with $CHCl_3$, and 5·3 g. of the amine crystallised from the cooled extract. Addition of NH_3 aq. to a 0·2N-HOAc extract of the residue from the $CHCl_3$ gave a further 2·2 g. (total yield, 85%). The *amine* crystallised from C_6H_6 in transparent yellow prisms, m. p. 152° (Found : C, 80·8; H, 5·8; N, 13·2. $C_{14}H_{12}N_2$ requires C, 80·75; H, 5·75; N, 13·45%). The base dissolved in dil. HCl aq. to a yellow solution, but addition of conc. HCl aq. diminished the colour and produced a white cryst. ppt., presumably of dihydrochloride. The solution in acids could be diazotised and then coupled with sodium β-naphthoxide aq. to yield a deep red azo-derivative. The amine reacted vigorously with Ac_2O and the *acetyl* compound, pptd. by NH_3 aq., crystallised from EtOH in pale yellow, flat prisms, m. p. 240—242°. Its solubility in dil. acid may be attributed to the presence of the tertiary N atom (Found : C, 76·5; H, 5·95; N, 10·95. $C_{16}H_{14}ON_2$ requires C, 76·8; H, 5·6; N, 11·2%).

3-*Acetamido*-9 : 10-*dimethylphenanthridinium methosulphate*, obtained when Me_2SO_4 (3 g.) reacted with the foregoing acetyl compound (4·5 g.) in hot $PhNO_2$ (25 c.c.), crystallised in minute yellow needles (6·2 g.; decomp. *ca.* 255°); it was insol. in org. non-hydroxylic solvents, moderately sol. in EtOH to a green fluorescent solution, but very sol. in H_2O (Found : C, 57·55; H, 5·2; N, 7·2; S, 8·35. $C_{18}H_{20}O_5N_2S$ requires C, 57·4; H, 5·3; N, 7·45; S, 8·5%).

3-*Amino*-9 : 10-*dimethylphenanthridinium Chloride*.—Hydrolysis of the methosulphate (4 g.) was effected readily with hot 5N-HCl in 1 hr. On partial neutralisation with NH_3 aq., the liquid filled with golden-yellow needles of the *chloride* (2·5 g.). This salt was insol. in org. non-hydroxylic solvents, and only very slightly sol. in Me_2CO or EtOH; it crystallised readily from hot H_2O with $2H_2O$, which was lost at 100° or over $CaCl_2$ in a vac. desiccator; the anhyd. salt was hygroscopic, m. p. *ca.* 275° (decomp.) (Found, in air-dried salt : C, 61·05; H, 6·0; Cl, 12·05. $C_{15}H_{15}N_2Cl,2H_2O$ requires C, 61·1; H, 6·45; Cl, 12·05%).

2-o-*Nitrobenzamido*-5-*nitrodiphenyl*.—Mol. quantities of 5-nitro-2-xenylamine and *o*-nitrobenzoyl chloride were heated in C_5H_5N for 30 mins. Addition of H_2O pptd. a gum, which hardened when heated successively with conc. HCl aq. and H_2O. It crystallised from HOAc in thick, light brown prisms, or from EtOH in yellow plates, m. p. 167° (Found : N, 11·55. $C_{19}H_{13}O_5N_3$ requires N, 11·55%).

3-*Nitro*-9-o-*nitrophenylphenanthridine*.—The foregoing amide reacted vigorously with $POCl_3$ with evolution of HCl and rapid darkening. The dark

brown powder obtained by the usual process could not be purified by solvents, but sublimation at 250°/5 mm. gave a small yield of pale yellow cubic crystals, leaving a bulky carbonaceous residue. The *dinitro*-compound was almost insol. in EtOH but more soluble in C_6H_6; it was insol. in acids; it crystallised best from boiling C_7H_8 in pale yellow, transparent parallelepipeds, m. p. 227° (Found: N, 12·1. $C_{19}H_{11}O_4N_3$ requires N, 12·15%).

Phenanthridine.—Form-*o*-xenylamide (30 g.) and $ZnCl_2$ sticks (75 g.) were heated together for 7 hrs.; steam and CO escaped steadily at 220°, and reaction was completed at 280°. The melt was extracted with hot H_2O, and the yellow horny residue, still containing Zn compounds, was boiled under reflux with methylated spirit (50 c.c.). The turbid yellow solution was poured into 5*N*-NaOH (200 c.c.) to liberate an oil which was extracted with Et_2O and dried over anhyd. Na_2SO_4. After evaporation of solvent, the residual oil was warmed with Ac_2O (20 c.c.) and poured into hot *N*-HCl (100 c.c.); acet-*o*-xenylamide (*ca.* 18 g.) was pptd., and addition of NH_3 aq. to the filtrate liberated phenanthridine (11 g.; 42% yield). This base was purified by adding a slight excess of conc. H_2SO_4 to its alc. solution; the liquid filled with colourless crystals of sulphate, which was very sol. in H_2O. Phenanthridine crystallised from petroleum (b. p. 60—80°) in opaque white needles, m. p. 105—106° (Found: N, 8·0. Calc. for $C_{13}H_9N$: N, 7·8%).

When a solution of the base in hot 3*N*-HNO_3 was cooled, transparent, pale yellow prisms of a *dinitrate* separated (Found: NO_3, 36·05, 36·0. $C_{13}H_9N,2HNO_3,2H_2O$ requires NO_3, 36·35%). By crystn. from EtOH, long, silky, almost colourless needles of the *nitrate* were obtained, m. p. 169—171° (decomp.) (Found: NO_3, 25·4. $C_{13}H_9N,HNO_3$ requires NO_3, 25·6%). The same product was obtained from the abnormal nitrate by stirring it into Me_2CO, or by adding a small vol. of H_2O, the prisms slowly disintegrating and giving place to a voluminous mass of needles.

Phenanthridine, unaffected by hot conc. HNO_3, was nitrated by adding anhydrous nitrate (24 g.) slowly to conc. H_2SO_4 (48 c.c.) at 0°, the mixture being heated finally to 100° and left over-night. A mixture of mono-nitrates was pptd. by addition of NH_3 aq. after dilution with ice. The following were obtained by fractional crystn. from EtOH: a slightly sol. product which sublimed at 220°/6 mm.; opaque yellow needles, m. p. 260—262° after previous softening, from AcOH (Found: N, 12·45. $C_{13}H_8O_2N_2$ requires N, 12·5%); yellow prisms (4 g.), m. p. 160—163°, separated mechanically (Found: N, 12·5%); and, in very small yield, yellow needles, m. p. 156—158° (Found by micro-analysis: N, 12·7, 12·65%).

9-*Aminophenanthridine.*—(A) The success of this expt. depended on the quality of the $NaNH_2$ employed; in one attempt an 80% yield of amine was obtained, but the following is a more typical example. Xylene (25 c.c.) previously dried over Na, phenanthridine (5 g.), and $NaNH_2$ (5 g.), ground to a fine powder in a warm mortar, were introduced into a large glass tube connected to a gas-holder. Before heating, air was replaced by H; at 110° liberation of H commences, to become brisk at 120—130°, 100 c.c. of gas being rapidly collected. After 6 hrs., 200 c.c. of gas having been obtained, the black pasty product was decomposed with ice. A yellow suspension (3·2 g.; 60% yield), contained in the xylene layer, crystallised from EtOH in transparent parallelepipeds, m. p. 195·5° (Found: C, 80·25; H, 5·25; N, 14·15. $C_{13}H_{10}N_2$ requires C, 80·4; H, 5·15; N, 14·45%). The colour, which was traced to an impurity (*vide infra*), may be removed by dissolving the

amine in dil. AcOH, decolorising the solution with charcoal, and re-pptn. with NH_3 aq. The *amine* now crystallised in colourless prisms.

After extraction with dil. HCl aq. and evap. to dryness, the xylene mother-liquor left a negligible residue. The acid extract yielded chiefly unchanged phenanthridine, with no appreciable by-product.

(B) A stream of dry NH_3 was led through a solution of phenanthridine (7 g.) in redist. $NPhMe_2$ (20 c.c.) containing clean Na (2 g.) in suspension; vigorous reaction commenced at 90°, the mixture becoming black and pasty. The temp. was raised slowly to 160°, and after 3 hrs. the product was cooled and decomposed with H_2O. The $NPhMe_2$ layer contained a yellow suspension (6·5 g.; to which was added a further 0·8 g. by evap. of the mother-liquor). This product dissolved in hot 2*N*-HCl to a deep crimson solution, leaving only a trace of amorphous residue. By dissolution in hot *N*-HOAc it gave a light red solution which was decolorised (charcoal) and then yielded white 9-aminophenanthridine (*ca.* 6·3 g.) on neutralisation, identical with the foregoing prep. A slight brown residue, insol. in HOAc, crystallised from $CHCl_3$ in strongly refractive brown needles. This weakly basic substance is unmolten at 310°; its solution in HOAc and mineral acids is crimson; it is slightly sol. in C_6H_6, EtOH, and $CHCl_3$ to yellow solutions of brilliant fluorescence. A trace added to conc. H_2SO_4 produced an intense laurel-green colour, changed by progressive dilution with H_2O to blue, violet, and then red.

The *acetate* and *lactate*, prepared by dissolving the amine in a slight excess of the hot dil. acid, crystallised in white needles, m. p. respectively 206—209° and 202—204° (decomp.) (Found, for the acetate: N, 11·1. $C_{13}H_{10}N_2,C_2H_4O_2$ requires N, 11·0%. For the lactate: N, 9·95. $C_{13}H_{10}N_2,C_3H_6O_3$ requires N, 9·85%).

Phenanthridone from 9-Aminophenanthridine.—$NaNO_2$ in a min. of H_2O was added to a paste of 9-aminophenanthridine sulphate in 3*N*-H_2SO_4 at 0°. A slow reaction occurred, and after many hrs. the mixture was boiled and filtered hot. The residue, after washing with hot 3*N*-H_2SO_4, was sublimed at 240°/7 mm., giving white prismatic needles, m. p. 291—293° alone or in admixture with authentic phenanthridone (*vide infra*).

Acetyl-9-aminophenanthridine.—Ac_2O in slight excess and the amine in C_5H_5N (16 c.c.) were heated together at 100° for a few mins. On cooling, the *acetyl* compound separated as a voluminous mass of white needles, m. p. 193·5°, moderately sol. in EtOH or C_6H_6 (Found: C, 76·5; H, 5·1; N, 11·9. $C_{15}H_{12}ON_2$ requires C, 76·3; H, 5·15; N, 11·85%). Although sol. in dilute acids, this compound could not be recovered from such solutions owing to extensive hydrolysis. For this reason acetylation of 9-aminophenanthridine with Ac_2O in absence of C_5H_5N generally leads to a mixture of base and acetyl derivative.

The interaction of acetyl-9-aminophenanthridine in hot $PhNO_2$ with Me_2SO_4 did not lead to the isolation of a cryst. product. The acetyl compound was recovered unchanged after being heated in a sealed tube for 3 hrs. at 110° with MeI and MeOH.

o-Xenylcarbamide.—*o*-Xenylamine (30 g.) in 750 c.c. of C_7H_8 reacted rapidly with $COCl_2$ during 2 hrs., and the liquid product was distilled under reduced press. After C_7H_8 had evaporated, *o*-xenylcarbimide distilled at 130°/5 mm. as a pale yellow oil in quantitative yield. It reacted vigorously with NH_3 aq., with formation of white cryst. *o-xenylcarbamide*, slightly sol. in boiling C_6H_6, but crystallising from EtOH in clusters of colourless prisms, m. p.

157—158·5° (Found: C, 73·05; H, 6·0; N, 13·15. $C_{13}H_{12}ON_2$ requires C, 73·6; H, 5·65; N, 13·2%). When *o*-xenylcarbimide and MeOH were heated at 100° for 1 hr., *methyl o-xenylcarbamate* was formed, which set to a cryst. mass on cooling, m. p. 61° (Found: N, 6·1. $C_{14}H_{13}O_2N$ requires N, 6·15%).

3 G. of *o*-xenylcarbamide were fused with $ZnCl_2$ sticks (10 g.) at 250° for 3 hrs. $ZnCl_2$ was removed by successive extractions with hot dil. HCl aq. and H_2O; the white residue (0·8 g.) sublimed in the white prismatic needles characteristic of phenanthridone (Found: C, 80·0; H, 4·5. Calc. for $C_{13}H_9ON$: C, 80·0; H, 4·6%).

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