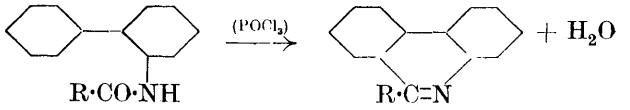
CCCXXXV.—*Researches in the Phenanthridine Series. Part I. A New Synthesis of Phenanthridine Homologues and Derivatives.*

By Gilbert T. Morgan and Leslie Percy Walls.

Most of the work on phenanthridine was done between 1889 and 1905 by Pictet and his co-workers, who developed a method of preparation (Pictet and Hubert, *Ber.*, 1896, **29**, 1182) in which acyl-*o*-xenylamines were dehydrated by fusion with zinc chloride. The disadvantages of this method are those inherent in the use of zinc chloride: long heating, wasteful methods of purification leading to poor yields, and inapplicability to compounds containing reactive substituents such as nitro-groups.

An improved method of preparation of phenanthridine derivatives is now described which obviates these difficulties. The dehydration of acyl-*o*-xenylamines has been found to proceed smoothly by refluxing them with phosphorus oxychloride; the reaction is fairly general and has been used successfully in the preparation of alkyl-, chloroalkyl-, phenyl-, and nitrophenyl-phenanthridines. It fails, however, in the case of formyl-*o*-xenylamine, so that phenanthridine itself cannot be prepared in this manner.

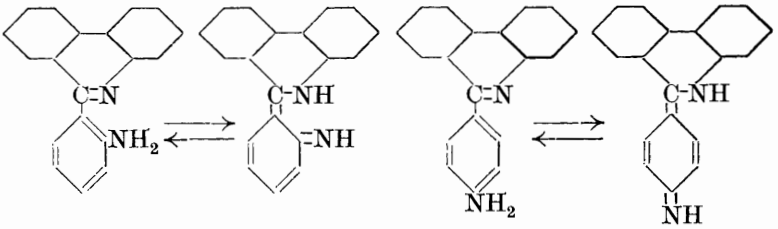


Application of phosphorus oxychloride to the preparation of 9-ω-*chloromethylphenanthridine* is noteworthy in that a few months ago the first successful application of the Bischler–Napieralski reaction to a substituted chloro-acetamide was recorded (Child and Pyman, this vol., p. 37). In addition, the preparation of methyl-, ethyl-, and phenyl-phenanthridines and 9-o-, 9-m-, and 9-p-*nitrophenyl-phenanthridines* is described in the experimental part. These nitro-compounds are well-defined stable substances which are soluble in fairly concentrated acid.

Pictet (*Annalen*, 1892, **266**, 151) records the reduction of phenanthridine to 9 : 10-dihydrophenanthridine by tin and hydrochloric acid, and since the reduction of 9-nitroacridone by sodium amalgam in alcohol resulted in the formation of 9-amino-5 : 10-dihydroacridine (Clemo, Perkin, and Robinson, J., 1924, **125**, 1784), it seemed desirable to employ a method of reduction of the nitrophenylphenanthridines which did not involve hydrogenation of the pyridine ring. This end was attained with iron and acidified water, reagents which, although not reacting with phenanthridine itself, reduced the isomeric 9-nitrophenylphenanthridines smoothly to the corresponding *amines*, obtained in this way as crystalline solids dissolving in dilute acid to diazotisable solutions. The soluble diazonium salts coupled with alkaline β-naphthol solution to yield red azo-compounds.

A difference was exhibited in the colours of the acidic solutions of the isomeric bases, for whereas the *o*- and *p*-compounds furnished orange-red tints, the *m*-isomeride gave nearly colourless solutions; the intensity of colour was reduced by the addition of concentrated mineral acid. The molecules of the *o*- and *p*-compounds contain the possibility of quinonoid tautomerism in which reversal of a long chain of conjugated linkages is involved (Watson and Meek,

J., 1915, **107**, 1567), but a similar type of quinonoid structure cannot be postulated for the *m*-compound.



The effect of solution in dilute acids is to bring the selective absorption into the range of visible colour; addition of concentrated mineral acid causes the attachment of a proton to each terminal basic group with suppression of tautomerism; in any concentration the weaker acetic acid does not produce this effect. It is noteworthy that 9-*o*- and 9-*p*-nitrophenylphenanthridines are yellow, whereas the *m*-compound is white; 9-*o*-aminophenylphenanthridine is yellow.

The colourless *acetyl* compounds derived from these bases are conveniently converted into quaternary salts by the methods employed so successfully in the acridine series by Ullmann and Marić (*Ber.*, 1901, **34**, 4307); addition of methyl sulphate to their solutions in hot nitrobenzene induced crystallisation of the quaternary methosulphate. 9-o-*Acetamidophenyl*-10-*methylphenanthridinium methosulphate* forms buff-coloured needles, and the m-*isomeride* almost colourless needles. The p-*compound*, a yellow crystalline substance containing nitrobenzene of crystallisation, is freed from combined solvent by crystallisation from alcohol. Hydrolysis of the acetyl methosulphates proceeds readily when they are refluxed with concentrated hydrochloric acid, but the 9-*aminophenyl*-10-*methylphenanthridinium chlorides*, unlike the analogous acridine compounds (Benda, *Ber.*, 1912, **45**, 1787), do not separate on cooling; they are precipitated on addition of ammonia until the solution is approximately of p_H 5, and are readily purified by crystallisation from hot water. The *o*-compound occurs in orange prisms, the *m*-isomeride in flat yellow needles, and the *p*-isomeride in scarlet plates. The quaternary salts are moderately easily soluble in hot and slightly soluble in cold water, but more soluble in mineral acid. These three quaternary chlorides have been tested on trypanosomes by Professor Warrington Yorke, who finds that they have no trypanocidal potency.

EXPERIMENTAL.

Acyl-o-*xenylamines.*

Acetyl- and *propionyl*-o-*xenylamines* were obtained by warming the base for a few minutes with the appropriate acid anhydride,

and pouring the mixture into water. Although the method has been regarded as unsatisfactory for this series (Scarborough and Waters, J., 1927, 89), in our experiments both compounds were obtained quantitatively, and crystallised in colourless prismatic needles which for the acetyl compound melted at 120° (Found : C, 79·65; H, 6·3. $C_{14}H_{13}ON$ requires C, 79·6; H, 6·15%), and for the propionyl at 67° (compare Pictet and Hubert, *loc. cit.*).

*Chloroacetyl-*o*-xenylamine.*—A solution of 40 g. of *o*-xenylamine in a large volume of ether (*ca.* 500 c.c.) was cooled in ice and stirred while being treated with 14 g. of chloroacetyl chloride. The precipitated *o*-xenylamine hydrochloride was washed with ether; the combined ethereal filtrates after successive extraction with dilute acid and water, were dried over anhydrous potassium carbonate. On evaporation of the ether, crystalline *chloroacetyl-*o*-xenylamine* was left (28 g.; 93% of the theoretical yield) sufficiently pure for the purpose in view. It crystallised from ligroin or alcohol in flat colourless prisms, m. p. 98·5° (Found : N, 5·75; Cl, 14·05. $C_{14}H_{12}ONCl$ requires N, 5·7; Cl, 14·45%).

Benzoyl-*o*-xenylamine, prepared by the Schotten–Baumann method, was obtained in small needles, m. p. 86° (compare Pictet and Hubert, *loc. cit.*).

o-*Nitrobenzoyl-*o*-xenylamine.*—To a solution of 24 g. of *o*-xenylamine in 15 c.c. of dry pyridine were added slowly 25 g. of *o*-nitrobenzoyl chloride, and after being heated on the steam-bath for 1 hour the product was poured into water. On crystallisation from spirit, 37 g. (82% yield) of small, pale yellow, prismatic needles were obtained, m. p. 129—131° (Found : N, 8·9. $C_{19}H_{14}O_3N_2$ requires N, 8·8%).

This method, using the appropriate nitrobenzoyl chloride, was employed in the preparation of m-*nitrobenzoyl-*o*-xenylamine* (41 g.; yield, 91%), colourless prismatic needles, m. p. 134° (Found : N, 9·05%), and p-*nitrobenzoyl-*o*-xenylamine* (39 g.; yield, 86%), pale yellow, prismatic needles, m. p. 158·5° (Found : N, 8·65%).

Alkyl- and Aryl-phenanthridines.

9-*Methylphenanthridine.*—Acetyl-*o*-xenylamine (5 g.) was heated gently with twice its weight of freshly distilled phosphorus oxychloride in a dry atmosphere. The vigorous effervescence of hydrogen chloride subsided after a few minutes, but slow ebullition was continued for 1 hour. Excess of phosphorus oxychloride was distilled away under reduced pressure, and the residual gum warmed with dilute hydrochloric acid (80 c.c. *N*; an excess required owing to the low solubility of 9-methylphenanthridine hydrochloride). The acid solution, after filtration from a small insoluble residue,

was basified with ammonia, and the liberated oil extracted with ether. The extract was dried over anhydrous sodium sulphate, the ether evaporated, and the residue crystallised from a large volume of alcohol containing hydrochloric acid. 9-Methylphenanthridine hydrochloride was obtained in almost colourless, felted needles, from which the base was liberated as a white solid (3·2 g.; yield, 70%), conveniently crystallised from petroleum (b. p. 60—80°) in white opaque needles, m. p. 84° (Found: N, 7·5, 7·25. Calc. for $C_{14}H_{11}N$: N, 7·25%).

For purposes of comparison, 9-methylphenanthridine was prepared by Pictet's method (Pictet and Hubert, *loc. cit.*), a more convenient method of purification being employed. Ten g. of acetyl-*o*-xenylamine and 30 g. of zinc chloride sticks were heated slowly to 250—300° and maintained between these limits for 3 hours. Excess of zinc chloride was extracted from the mass by lixiviation with water, and the horny residue, which still contained zinc compounds, was extracted with alcohol. This solution was poured into concentrated aqueous sodium hydroxide, and the basic oil, after being separated in ether and dried, was distilled under reduced pressure. The fraction (2½ g.) collected above 200°/14 mm. solidified; it crystallised from petroleum (b. p. 60—80°) in opaque white needles, m. p. 83—83·5° (alone and in admixture with the foregoing preparation).

9-Ethylphenanthridine was prepared from propionyl-*o*-xenylamine (5 g.) and phosphorus oxychloride (10 g.) as described for the methyl compound. The crude product (4·3 g.), directly crystallised from petroleum (b. p. 40—60°), gave the base in fine colourless plates (3·6 g.; yield, 80%), m. p. 56·5° (Found: C, 87·3; H, 6·45; N, 6·9. Calc. for $C_{15}H_{13}N$: C, 86·95; H, 6·3; N, 6·8%).

9-ω-*Chloromethylphenanthridine*.—Chloroacetyl-*o*-xenylamine (27 g.) and phosphorus oxychloride (54 g.) reacted vigorously. The residual gum after removal of excess of phosphorus oxychloride was extracted several times with hot dilute sulphuric acid, the sulphate of the base being more soluble than the hydrochloride. The extract on neutralisation yielded a mass of white needles (20 g.; yield, 80%), m. p. 134° after recrystallisation from alcohol. The *chloro*-compound was very soluble in benzene, moderately easily in hot alcohol, but much less in petroleum; it dissolved readily in aqueous dilute mineral acids, but was insoluble in phosphoric and dilute acetic acids (Found: C, 73·6; H, 4·45; N, 6·25; Cl, 15·4. $C_{14}H_{10}NCl$ requires C, 73·9; H, 4·4; N, 6·15; Cl, 15·6%). 9-Phenylphenanthridine was prepared similarly from benzoyl-*o*-xenylamine (4 g.) and phosphorus oxychloride. Neutralisation of the acid extract gave the base (2·9 g.; yield, 75%), which was

soluble in dilute phosphoric acid. It crystallised from benzene, alcohol, or petroleum in white plates, m. p. 105—106·5° (Found : N, 5·55. Calc. for $C_{19}H_{13}N$: N, 5·5%). Pictet and Hubert (*loc. cit.*) gave m. p. 109°, but a specimen prepared by their method melted at 105—106° and gave no depression on admixture with our product.

9-o-*Nitrophenylphenanthridine.*—*o*-Nitrobenzoyl-*o*-xenylamine (20 g.) was refluxed for 2 hours with phosphorus oxychloride (40 g.). The initial vigorous evolution of hydrogen chloride slackened after 20 minutes; the solution deepened in colour from pale yellow to dark brown. Removal of excess of oxychloride left a gum, which was heated with 2*N*-caustic soda solution. On cooling, a brown crystalline solid was obtained which was boiled with an excess of 2*N*-sulphuric acid (250 c.c. in three portions; the hydrochloride is less soluble); a residue of tar was neglected. Addition of ammonia to the extract precipitated a buff-coloured solid (15·5 g.). Crystallisation from benzene gave yellow leaflets which effloresced on exposure and had an indefinite melting point. The presence of benzene of crystallisation appeared probable, and by crystallisation from alcohol pale yellow prisms of sharp melting point 122·5° were obtained (14 g.; yield, 74%). The *nitro*-compound, which was quite stable to light and to moist air, was very soluble in benzene and acetone, less soluble in alcohol, and almost insoluble in petroleum; it gave crystalline salts from dilute mineral acids (2*N*) (Found : C, 75·85; H, 4·3; N, 9·25. $C_{19}H_{12}O_2N_2$ requires C, 76·0; H, 4·0; N, 9·35%).

9-m-*Nitrophenylphenanthridine* was prepared similarly from *m*-nitrobenzoyl-*o*-xenylamine (20 g.), except that the product was worked up differently owing to its lower solubility in acid. In this case there was no formation of tarry products. The gum left after removal of the excess of phosphorus oxychloride, when heated with caustic soda solution, was converted into a white powder (18 g.), which crystallised from benzene–alcohol in long felted white needles of 9-*m*-nitrophenylphenanthridine (11·5 g.; yield, 61%), m. p. 172°; the mother-liquor contained unchanged acyl compound. Crystallised from a large volume of alcohol, the nitro-compound separated in transparent white prismatic needles of the same melting point (Found : C, 75·95; H, 4·15; N, 9·35%).

9-p-*Nitrophenylphenanthridine.*—Incomplete ring closure, occurring also in the preceding preparation, made the purification of this substance more difficult. *p*-Nitrobenzoyl-*o*-xenylamine (13 g.) was boiled for 3 hours with a large excess of phosphorus oxychloride (65 g.). By working up the product by the method described for the *m*-compound, a pale yellow powder was obtained which was

crystallised from a mixture of equal volumes of alcohol and benzene. The first crop (3·2 g.) consisted of pure 9-p-*nitrophenylphenanthridine*; evaporation of the mother-liquor left a mixture of this substance and *p*-nitrobenzoyl-*o*-xenylamine, which was boiled again with phosphorus oxychloride and worked up in the same way. By a repetition of this process, eventually 8 g. of pure 9-*p*-nitrophenylphenanthridine were obtained (yield, 65%) in long felted yellow needles, m. p. 192°. This nitro-compound was slightly soluble in 2*N*-hydrochloric acid; it dissolved readily in hot benzene or acetone, but was much less soluble in alcohol (Found: C, 76·1; H, 4·2; N, 9·45%).

Aminophenylphenanthridines.

9-o-*Aminophenylphenanthridine.*—9-*o*-Nitrophenylphenanthridine (10 g.) and iron filings (10 g.) were ground together and heated with acidified dilute alcohol. Reduction commenced on boiling, and black iron oxide formed; after 6 hours' ebullition, excess of chalk was added. The dried residue after draining from water was extracted in a Soxhlet apparatus with chloroform; the extract on cooling deposited the base in transparent yellow plates (6 g.; 2nd crop, 1·8 g.; yield, 90%). The pure *base* crystallised from benzene, and melted at 168·5° (Found: C, 84·9; H, 5·25; N, 10·2. $C_{19}H_{14}N_2$ requires C, 84·45; H, 5·2; N, 10·35%).

The amine dissolved in boiling dilute hydrochloric acid to an orange-red solution which deposited, on cooling, transparent brownish-yellow prisms of the hydrochloride. On addition of sodium nitrite to a hydrochloric acid solution, a bright yellow flocculent precipitate of the diazonium salt formed which dissolved on dilution; this solution gave with alkaline β-naphthol a red precipitate of the azo-compound. The base was acetylated by warming with acetic anhydride for 5 minutes at 100° and pouring the solution into water. The *acetyl* compound, obtained in colourless cubes by crystallisation from benzene, contained solvent of crystallisation (Found: loss of weight on heating, 11·55, 11·35. $C_{21}H_{16}ON_2,\frac{1}{2}C_6H_6$ requires loss, 11·1%). The solvent-free product melted at 185° (Found: C, 80·75; H, 5·05; N, 8·9. $C_{21}H_{16}ON_2$ requires C, 80·75; H, 5·15; N, 9·0%).

9-m-*Aminophenylphenanthridine* was obtained in good yield by the reduction of the nitro-compound in acidified dilute alcohol with iron; the base was separated from unreduced nitro-compound by extraction of the crude product with hot 0·5*N*-hydrochloric acid. It crystallised from a large volume of benzene in clumps of discoloured irregular prisms, m. p. 159—161° (Found: C, 84·25; H, 5·6; N, 10·0. $C_{19}H_{14}N_2$ requires C, 84·45; H, 5·2; N, 10·35%).

By warming the base with acetic anhydride for 5 minutes and pouring the solution into water, the *acetyl* compound was obtained. It was crystallised by dissolving it in pyridine at 100° and adding an equal volume of boiling petroleum (b. p. 80—100°); on cooling, colourless prisms, m. p. 237·5°, separated (Found: C, 80·75; H, 5·3; N, 8·9. $C_{21}H_{16}ON_2$ requires C, 80·75; H, 5·15; N, 9·0%).

9-p-*Aminophenylphenanthridine* was prepared similarly from the 9-*p*-nitro-compound. It proved difficult to purify by crystallisation and was converted directly into the *acetyl* compound by warming with acetic anhydride. After removal of coloured impurities by heating with benzene, it crystallised from pyridine and petroleum in colourless prismatic needles, m. p. 219° (Found: C, 81·25; H, 5·2; N, 9·15. $C_{21}H_{16}ON_2$ requires C, 80·75; H, 5·15; N, 9·0%). By crystallisation from alcohol, irregular prisms were obtained which lost solvent of crystallisation at 120—130° and then melted sharply at 219°.

Hydrolysis of 9-p-*acetamidophenylphenanthridine.* When a solution of this compound in alcohol containing 10% hydrochloric acid was boiled, the colour deepened to orange and an intractable gelatinous complex containing acid separated. Hydrolysis could not be effected by this method. The acetyl compound (3 g.) was boiled with 50 c.c. of alcohol containing 10% caustic potash; hydrolysis proceeded smoothly and after 1 hour crystals of the base began to separate. After 3 hours, most of the alcohol was removed by evaporation, excess of water added, and the crystalline product collected and dried. It was slightly soluble in benzene and chloroform, moderately easily soluble in alcohol, and very soluble in nitrobenzene, aniline, and pyridine. It was conveniently recrystallised from pyridine–petroleum (b. p. 80—100°), forming clusters of small, felted, slightly discoloured needles, m. p. 197—199° (Found: C, 84·45; H, 4·9; N, 10·3. $C_{19}H_{14}N_2$ requires C, 84·45; H, 5·2; N, 10·35%). The base dissolved in dilute acid to a deep orange-red solution; the colour was repressed by concentrated mineral acid but not by acetic acid.

Quaternary Salts of the Phenanthridine Series.

9-o-*Acetamidophenyl*-10-*methylphenanthridinium Methosulphate.*—9-*o*-Acetamidophenylphenanthridine (5 g.) was dissolved in nitrobenzene (30 c.c.), and the solution boiled to expel moisture. The temperature was allowed to fall slightly, and methyl sulphate (2·2 g.) added with shaking. Heat was liberated and the colour of the solution deepened to red. After a few minutes, buff-coloured needles separated rapidly; they were drained and washed with benzene and then with ether (yield, 5·5 g.). The quaternary *salt*

was moderately easily soluble in water or alcohol, but almost insoluble in organic non-hydroxylic solvents. It melted at *ca.* 225° (decomp.) but sintered and darkened at a lower temperature (Found : C, 63·15; H, 5·0; N, 6·45; S, 7·1. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·0; N, 6·4; S, 7·3%).

9-o-*Aminophenyl*-10-*methylphenanthridinium Chloride*.—The quaternary acetyl compound (4 g.) was refluxed for 1 hour with 5*N*-hydrochloric acid (18 c.c.). No crystals separated from the cold yellow solution, but when ammonia was added dropwise until neutrality was almost attained (about p_H 5) a yellow precipitate formed which redissolved on boiling to an orange-red solution. Clusters of orange-yellow prisms separated on cooling (2·7 g.). The *salt* was moderately easily soluble in hot water, but only slightly so in cold; it was more soluble in mineral acid. When heated above 170°, it became deep red and sintered, but melted fairly sharply at 226° with vigorous decomposition (Found : C, 71·3; H, 5·5; N, 8·3; Cl, 10·4. $C_{20}H_{17}N_2Cl,H_2O$ requires C, 70·9; H, 5·6; N, 8·3; Cl, 10·5%. $C_{20}H_{17}N_2Cl$ requires C, 74·9; H, 5·3; N, 8·75; Cl, 11·1%).

9-m-*Acetamidophenyl*-10-*methylphenanthridinium methosulphate*, prepared in the same way as its isomeride, separated from nitrobenzene solution in almost colourless, prismatic needles, which were recrystallised from alcohol. The quaternary salt became yellow at 170° and melted at *ca.* 209° (decomp.) (Found : C, 63·3; H, 5·1; N, 6·2; S, 7·1. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·0; N, 6·4; S, 7·3%).

9-m-*Aminophenyl*-10-*methylphenanthridinium chloride*, obtained by hydrolysis of the preceding compound, separated from water as flat yellow needles of similar properties to its isomeride. It deepened in colour at 160°, sintered rapidly at 218°, and melted at 222° (decomp.) (Found : C, 70·8; H, 5·65; N, 8·4; Cl, 10·35. $C_{20}H_{17}N_2Cl,H_2O$ requires C, 70·9; H, 5·6; N, 8·3; Cl, 10·5%).

9-p-*Acetamidophenyl*-10-*methylphenanthridinium Methosulphate*.—When 9-*p*-acetamidophenylphenanthridine (3·5 g.) in hot nitrobenzene (35 c.c.) was treated with methyl sulphate (1·5 g.) under the conditions already described, yellow transparent plates were precipitated (5·2 g.). The yield was greater than that calculated from the sum of the weights of the reactants, and when boiled with water the substance dissolved with liberation of nitrobenzene. Crystallisation of the complex from alcohol gave a solvent-free product in yellow prisms (3·5 g.), and from the mother-liquor a good yield of nitrobenzene was obtained by distillation in steam. The first product was evidently a double *compound* of the quaternary salt and nitrobenzene—a hypothesis confirmed by an analysis for

nitrogen. The *salt* darkened at 170° and decomposed at *ca.* 228° (Found for the complex containing nitrobenzene: N, 7·4. $C_{23}H_{22}O_5N_2S,C_6H_5{\cdot}NO_2$ requires N, 7·5%. Found for the salt crystallised from alcohol: C, 63·2; H, 4·85; N, 6·15; S, 7·2. $C_{23}H_{22}O_5N_2S$ requires C, 63·0; H, 5·0; N, 6·4; S, 7·3%).

9-p-*Aminophenyl*-10-*methylphenanthridinium chloride* was prepared in the same way as its isomerides, which it resembled. It crystallised from hot water in clusters of scarlet plates, almost insoluble in cold water but very soluble in acid. It melted with vigorous decomposition at 247° after sintering at a lower temperature (Found: C, 71·25; H, 5·5; N, 8·5; Cl, 10·45. $C_{20}H_{17}N_2Cl,H_2O$ requires C, 70·9; H, 5·6; N, 8·3; Cl, 10·5%).

CHEMICAL RESEARCH LABORATORY,
TEDDINGTON, MIDDLESEX.

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