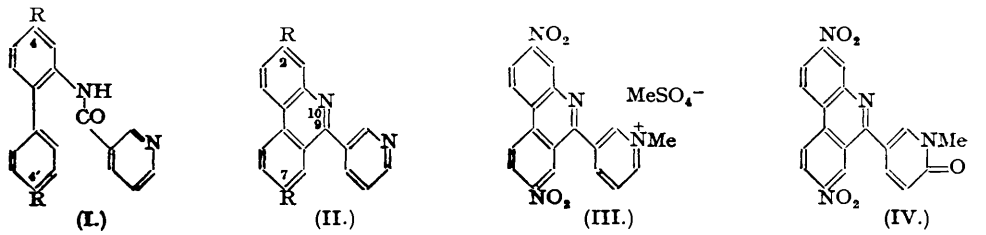
693. *Contributions to the Chemistry of Phenanthridine. Part II. The Preparation of 2 : 7-Diamino-9-3′-pyridylphenanthridine 1′ : 10-Dimethiodide.*

By V. Petrow and W. R. Wragg.

The synthesis of 9-3′-pyridylphenanthridines reported in Part I of this series has been extended by the preparation of some 2 : 7-disubstituted 9-3′-pyridylphenanthridine quaternary salts.

In Part I (*J.*, 1947, 1410) we described the preparation of some 9-3′-pyridylphenanthridines, together with a study of the structure of the derived monoquaternary salts. We now report the preparation of a 9-3′-pyridyl analogue of the potent trypanocide, Dimidium bromide, 2 : 7-diamino-9-phenylphenanthridine 10-methobromide (Walls, *J.*, 1945, 294).

Our initial experiments were directed towards the ring closure of 4 : 4′-biscarbethoxyamino-2-nicotinamidodiphenyl (I; R = $NH{\cdot}CO_2Et$) but all attempts in this direction proved unsuccessful; (I; R = $NH{\cdot}CO_2Et$) was recovered 64% unchanged after 1·25 hours' boiling with phosphoryl chloride (cf. Walls, *J.*, 1947, 67), and, although after 8 hours' boiling no unchanged material was recovered, yet no definite product could be isolated. Walls and Whittaker (*J.*, 1950, 41) have recently described the successful ring closure of (I; R = $NH{\cdot}CO_2Et$) by the action of phosphoryl chloride in nitrobenzene at 130°, but the yield of 2 : 7-biscarbethoxyamino-9-3′-pyridylphenanthridine (II; R = $NH{\cdot}CO_2Et$) obtained was rather low.



(I.) (II.) (III.) (IV.)

It was clear that relatively drastic conditions would be required for the alternative reaction the direct ring closure of 2-nicotinamido-4 : 4′-dinitrodiphenyl (I; R = NO_2). The nitro-substituents were expected to exert a considerable inhibitory influence (cf. Morgan and Walls, *J.*, 1932, 2225), especially as they were in the 4- and 4′-positions, and the reaction was expected to be additionally difficult owing to the presence of the pyridyl residue (Petrow and Wragg, *loc. cit.*). Nevertheless application of the improved techniques for the ring closure of 2-acylaminodiphenyls, which had just been developed by Barber, Bretherick, Eldridge, Holt, and Wragg (*J. Soc. Chem. Ind.*, 1950, **69**, 82), offered reasonable hope of success. The scope of the Morgan and Walls reaction had earlier been considerably widened by the introduction of nitrobenzene as solvent (Walls, *J.*, 1945, 294). Barber *et al.* (*loc. cit.*) found that striking improvements in yield and in the rate of reaction resulted from reduction of the proportion of phosphoryl chloride used, so that higher reaction temperatures were attained. They also established the value of Friedel–Crafts type catalysts in the reaction; *e.g.*, by use of 1·2 mols. of phosphoryl chloride in nitrobenzene, in the presence of 0·1 mol. of stannic chloride, the yield of 2 : 7-dinitro-9-phenylphenanthridine was raised from about 50% (cf. Walls, *loc. cit.*) to 95%, and the reaction time reduced from 20 to 2 hours.

Application of these new reaction conditions to (I; R = NO_2) led to the formation of (II; R = NO_2), but only in 20% yield. By increasing the amount of stannic chloride catalyst to

1·0 mol., however, 2 : 7-dinitro-9-3′-pyridylphenanthridine (II; R = NO_2) was obtained in yields exceeding 70%. A monoquaternary salt was obtained from (II; R = NO_2), which was assigned the structure of a 1′-methosulphate (III) (cf. Part I, *loc. cit.*), as (*a*) treatment with aqueous ammonia failed to precipitate an insoluble *pseudo*-base and (*b*) oxidation with aqueous alkaline potassium ferricyanide gave 9-(1 : 6-dihydro-6-keto-1-methyl-3-pyridyl)-2 : 7-dinitrophenanthridine (IV). (III) did not give a diquaternary salt even under drastic experimental conditions; its reduction with reduced iron in acidulated aqueous solution was likewise unsuccessful.

Reduction of (II; R = NO_2) with stannous chloride in concentrated hydrochloric acid gave 2 : 7-diamino-9-3′-pyridylphenanthridine (II; R = NH_2), converted into 2 : 7-biscarbethoxyamino-9-3′-pyridylphenanthridine (II; R = $NH{\cdot}CO_2Et$) by treatment with ethyl chloroformate and potassium carbonate in dilute aqueous acetone. The latter compound was best converted into the diquaternary salt by heating it with methyl sulphate at 180°. Hydrolysis of the resulting 2 : 7-biscarbethoxyamino-9-3′-pyridylphenanthridine 1′ : 10-dimethosulphate with 75% sulphuric acid, followed by treatment with potassium iodide, gave 2 : 7-diamino-9-3′-pyridylphenanthridine 1′ : 10-dimethiodide as shining black needles.

The structure of a pyridinium salt ascribed on grounds of analogy in Part I (*loc. cit.*) to the monomethosulphate derived from 7-nitro-9-3′-pyridylphenanthridine has now been confirmed by its oxidation to the corresponding 1-methyl-2-pyridone.

In experiments kindly performed by Miss R. M. Noble (Biological Division, May and Baker Ltd.) the average lethal dose (L.D.50) of 2 : 7-diamino-9-3′-pyridylphenanthridine 1′ : 10-dimethiodide for mice by subcutaneous injection was found to be 0·025 mg. per g. of body-weight. The compound was inactive against a *Trypanosoma rhodesiense* infection in mice, but had some effect, though not a curative action, at one-half the lethal dose given subcutaneously against a *T. congolense* infection. Accordingly, it was only feebly active compared with other phenanthridinium compounds.

Experimental.

(Semi-microanalyses are by Mr. S. Bance, B.Sc., A.R.I.C., Research Laboratories, May and Baker Ltd.)

4 : 4′-*Biscarbethoxyamino-2-nicotinamidodiphenyl* (I; R = $NH{\cdot}CO_2Et$) (cf. Walls and Whittaker, *J.*, 1950, 45).— A solution of nicotinoyl chloride hydrochloride [prepared from nicotinic acid (13 g., 1·2 mols.) and thionyl chloride] in boiling chlorobenzene (300 c.c.) was added in one portion to a boiling solution of 2-amino-4 : 4′-biscarbethoxyaminodiphenyl (30 g.) in chlorobenzene (150 c.c.), containing dimethylaniline (22 c.c., 2·0 mols.). After the vigorous reaction had subsided, the mixture was cooled, and ether (600 c.c.) added. Next day the supernatant liquor was decanted and aqueous ammonia (*d* 0·880; 100 c.c.) was added to the red solution obtained on dissolving the residue in a mixture of pyridine (250 c.c.) and methanol (250 c.c.). 4 : 4′-Biscarbethoxyamino-2-nicotinamidodiphenyl separated as a light brown crystalline product (24·3 g., 62%), m. p. 222—224° (decomp.) (Found : C, 64·1; H, 5·3; N, 12·5. Calc. for $C_{24}H_{24}O_5N_4$: C, 64·3; H, 5·4; N, 12·5%), unchanged by crystallisation from pyridine–methanol. Walls and Whittaker (*loc. cit.*) give m. p. 228—229° (decomp.).

2-*Nicotinamido*-4 : 4′-*dinitrodiphenyl* (I; R = NO_2).—Nicotinoyl chloride hydrochloride [prepared from nicotinic acid (79 g., 1·1 mols.)] was added during *ca.* 10 minutes to a stirred solution of 2-amino-4 : 4′-dinitrodiphenyl (150 g.) in dry pyridine (600 c.c.) heated to 110°, the rate of addition being controlled so as to maintain this internal temperature. The clear deep-red solution obtained was heated on the steam-bath for a further 10 minutes, and then diluted rapidly with 2N-ammonia (900 c.c.) added with vigorous stirring. The heavy crop of crystals which separated was filtered off as soon as the liquor had cooled to about 30°, so as to avoid contamination with traces of unchanged 2-amino-4 : 4′-dinitrodiphenyl which separated on storage. The product (184 g., 88%) was washed with water and then with acetone (200 c.c.). Crystallisation from 100 vols. (v/w) of chlorobenzene gave 2-*nicotinamido*-4 : 4′-*dinitrodiphenyl*, pale buff-coloured needles, m. p. 223—225° (Found : N, 15·1. $C_{18}H_{12}O_5N_4$ requires N, 15·35%).

2 : 7-*Dinitro*-9-3′-*pyridylphenanthridine* (II; R = NO_2).—A solution of the foregoing compound (7·28 g.) in nitrobenzene (80 c.c.) was dried by distilling off 10 c.c. of solvent. Stannic chloride (2·4 c.c., 1·05 mols.) was added to the solution under reflux at 214°; an immediate brisk reaction occurred and then the internal temperature became steady again at 212°. Phosphoryl chloride (3·5 c.c., 1·9 mols.) was then added in one portion, and heating continued for a further 4 hours under reflux at 204—205°. Hydrogen chloride was slowly evolved. The reaction mixture was cooled, poured into excess of dilute ammonia, and the nitrobenzene removed in steam. The precipitated solids were collected, dried, and extracted with boiling pyridine (200 c.c.). After hot filtration, the extract deposited 2 : 7-*dinitro*-9-3′-*pyridylphenanthridine* (5·15 g., 74%), forming small, glistening, brown prisms, m. p. 293—294° (Found : C, 62·7; H, 3·2; N, 16·3. $C_{18}H_{10}O_4N_4$ requires C, 62·4; H, 2·9; N, 16·2%), from pyridine.

2 : 7-*Diamino*-9-3′-*pyridylphenanthridine* (II; R = NH_2).—Stannous chloride (B.P.; 270 g.), dissolved in concentrated hydrochloric acid (850 c.c.), was added rapidly to a suspension of 2 : 7-dinitro-9-3′-pyridylphenanthridine (69 g.) in concentrated hydrochloric acid (1 l.) boiling under reflux. During the immediate vigorous reaction the suspended solid passed rapidly into solution, a red stannichloride commencing to separate after *ca.* 15 minutes. After a further 2 hours the reaction mixture was

cooled in ice. The stannichloride was collected after 12 hours and dissolved in water (1300 c.c.). The base was regenerated at 40° by addition with stirring of 50% sodium hydroxide solution (w/v; 1 l.). The precipitated solids were collected and dissolved in 2N-hydrochloric acid (800 c.c.), and ammonia solution (*d* 0·880) was added until the whole was alkaline to Congo-red. The filtered solution was stirred carefully into a large excess of 2N-aqueous ammonia heated on the steam-bath to 90°. The liberated base (48 g.) was purified by sublimation at 260°/0·1 mm., followed by crystallisation from chlorobenzene (5 l.). 2 : 7-*Diamino*-9-3′-*pyridylphenanthridine* separated in light brown prisms (34·7 g., 61%), m. p. 262—264° (Found, on sample dried at 190°/0·04 mm. for 2 hours : C, 75·4; H, 5·0; N, 19·4. $C_{18}H_{14}N_4$ requires C, 75·5; H, 4·9; N, 19·6%).

2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* (II; R = NH·CO_2Et).—Powdered 2 : 7-diamino-9-3′-pyridylphenanthridine (14·3 g.), dissolved in acetone (4 l.), was treated at 10° with anhydrous potassium carbonate (27·6 g., 4 mols.) dissolved in cold water (280 c.c.), added with vigorous stirring and followed immediately by ethyl chloroformate (14·4 c.c., 3 mols.). Cold water (1 l.) was added after 15 minutes' continued stirring at 10°. 2N-Acetic acid was then added to decompose the excess of potassium carbonate, followed by 2N-ammonia to restore slight alkalinity to litmus. The acetone was removed under reduced pressure, and the residual suspension boiled for 5 minutes to coagulate the precipitated yellow product. 2 : 7-Biscarbethoxyamino-9-3′-pyridylphenanthridine (16·7 g., 75%) separated from methanol (800 c.c.) in yellow needles which, when rapidly heated to 200°, melted to a yellow liquid. This resolidified and melted again with decomposition at 223—225° (Found, on sample dried at 95° : N, 12·5%). The *anhydrous derivative* formed a crystalline yellow powder, m. p. 223—225° (decomp.), from chlorobenzene [Found, on sample dried at 131°/10 mm. : OEt (Zeisel), 20·85. Calc. for $C_{24}H_{22}O_4N_4$: OEt, 20·9%]. Walls and Whittaker (*loc. cit.*) give m. p. 196—198° (decomp.). The compound gave a yellow fluorescence in ultra-violet light in concentrated sulphuric acid solution, and a blue fluorescence in methanol solution.

2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* 1′ : 10-*Dimethosulphate*.—2 : 7-Biscarbethoxyamino-9-3′-pyridylphenanthridine (2 g.) was dissolved at 120° in methyl sulphate (20 c.c.) and the solution heated with stirring to 180° during 10 minutes, kept thereat for 5 minutes, then cooled to 10° and stirred into dry ether (250 c.c.). The flocculent precipitated solids were collected, washed thoroughly with ether, and dissolved in the minimum of warm water. The solution was diluted to 200 c.c. with boiling alcohol, filtered, and kept overnight at 0°. 2 : 7-*Biscarbethoxyamino*-9-3′-*pyridylphenanthridine* 1′ : 10-*dimethosulphate dihydrate* separated as a red powder (2·4 g., 75%), m. p. (indef.) 225—240° (decomp.) [Found : C, 46·4; H, 5·5; N, 7·4; S, 9·2; OR (Zeisel), 9·15. $C_{28}H_{34}O_{12}N_4S_2,2H_2O$ requires C, 46·8; H, 5·3; N, 7·8; S, 8·9; OR, 8·9%].

2 : 7-*Diamino*-9-3′-*pyridylphenanthridine* 1′ : 10-*Dimethiodide*.—The foregoing dihydrate (1·4 g.), dissolved in water (1·4 c.c.) and concentrated sulphuric acid (2·8 c.c.), was heated at 120—130° for 30 minutes; the mixture was then poured on crushed ice (25 g.), and the resulting solution made just alkaline to litmus with aqueous ammonia (*d* 0·88). The deep-violet solution was stirred into potassium iodide (5 g.) in water (10 c.c.). The gummy purple precipitate was collected, dissolved in boiling water (20 c.c.), and added to a boiling solution of potassium iodide (5 g.) in water (4 c.c.). 2 : 7-*Diamino*-9-3′-*pyridylphenanthridine* 1′ : 10-*dimethiodide dihydrate* (0·7 g., 59%) was collected at 0°, and crystallised from aqueous methanol as very small glistening black needles, m. p. 220—230° (indef.) (Found, on sample dried *in vacuo* over KOH : N, 9·4; I, 41·9. $C_{18}H_{14}N_4,2CH_3I,2H_2O$ requires N, 9·2; I, 41·9%).

2 : 7-*Dinitro*-9-3′-*pyridylphenanthridine* 1′-*Methosulphate* (III).—A solution of 2 : 7-dinitro-9-3′-pyridylphenanthridine (3·46 g.) in dry nitrobenzene (50 c.c.) was treated with methyl sulphate (0·95 c.c., 1·0 mol.) for 30 minutes at 170—180°, then allowed to cool, and the 2 : 7-*dinitro*-9-3′-*pyridylphenanthridine* 1′-*methosulphate* (4·3 g., 92%) collected, m. p. 305—310° (decomp.) [Found : N, 11·7; S, 7·0; OMe (Zeisel), 6·7. $C_{18}H_{10}O_4N_4,(CH_3)_2SO_4$ requires N, 11·9; S, 6·8; OMe, 6·6%]. Crystallisation from water (180 c.c.) gave large, glistening, buff plates, of unchanged m. p.

9-(1′ : 6′-*Dihydro*-6′-*keto*-1′-*methyl*-3′-*pyridyl*)-2 : 7-*dinitrophenanthridine* (IV).—A solution of the foregoing compound (1 g.) in boiling water (200 c.c.) was treated at 60° with potassium ferricyanide (3 g.) dissolved in water (50 c.c.); 2N-sodium hydroxide (20 c.c.) was then added and the suspension rapidly heated to boiling. After 2 hours' reaction under reflux, the amorphous brown solids were collected and extracted with boiling pyridine (150 c.c.) for 2 hours. On cooling, the filtered extract deposited 9-(1′ : 6′-*dihydro*-6′-*keto*-1′-*methyl*-3′-*pyridyl*)-2 : 7-*dinitrophenanthridine* (0·57 g., 71%) which, on crystallisation from pyridine, formed a light brown powder, m. p. >360° (Found : C, 61·0; H, 3·3; N, 15·1. $C_{19}H_{12}O_5N_4$ requires C, 60·6; H, 3·2; N, 14·9%), insoluble in boiling N-hydrochloric acid.

9-(1′ : 6′-*Dihydro*-6′-*keto*-1′-*methyl*-3′-*pyridyl*)-7-*nitrophenanthridine*.—Oxidation of 7-nitro-9-3′-pyridylphenanthridine 1′-methosulphate (Petrow and Wragg, *loc. cit.*) with aqueous alkaline ferricyanide was carried out as described above for the 2 : 7-dinitro-compound. The crude 9-(1′ : 6′-*dihydro*-6′-*keto*-1′-*methyl*-3′-*pyridyl*)-7-*nitrophenanthridine* (65%) separated from pyridine in small yellow needles, m. p. 339—340° (Found : C, 68·9; H, 4·1; N, 12·9. $C_{19}H_{13}N_3O_3$ requires C, 68·9; H, 3·9; N, 12·7%), insoluble in boiling N-hydrochloric acid.

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