576. *The Search for Chemotherapeutic Amidines. Part XI.* Phenanthridines. Part II.*

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Derivatives of 9-phenylphenanthridine have been prepared and examined for trypanocidal activity.

SEVERAL years ago, stimulated by the work of Walls (*J.*, 1938, 389; 1945, 294), Barber, Gregory, Major, Slack, and Woolman (*J.*, 1947, 84) examined amidine analogues of 9-*p*-amidinophenyl-7-amino-10-methylphenanthridinium chloride (" Phenidium Chloride "). Although no pronounced trypanocidal activity was found, we have since modified 2 : 7-diamino-10-methyl-9-phenylphenanthridinium chloride (" Dimidium Chloride "; Walls, 1945, *loc. cit.*), another active trypanocide, in a similar manner and have prepared 2 : 7-diamidino-9-phenylphenanthridine dihydrochloride (I) and 2 : 7-diamidino-10-methyl-9-phenylphenanthridinium chloride dihydrochloride (II), both of which are slightly trypanocidal. Replacement of the 2 : 7-diamino-groups of 2 : 7-diamino-9-*p*-aminophenyl-10-methylphenanthridinium chloride (Walls and Whittaker, *J.*, 1950, 41) by halogen atoms also has a dystherapeutic effect and 2 : 7-dichloro-9-*p*-aminophenylphenanthridine (III) exhibits only slight biological activity. 2 : 7-Dibromo-9-*p*-nitrophenylphenanthridine and the corresponding methobisulphate have also been prepared.

2 : 7-Dicyano-9-phenylphenanthridine was obtained from the corresponding diamine (Walls, *J.*, 1945, 294) by the normal Sandmeyer procedure and gave a di-imino-ether hydrochloride on prolonged treatment with alcohol and dry hydrogen chloride. Reaction with saturated alcoholic ammonia gave the required diamidine dihydrochloride. With methyl sulphate in nitrobenzene, the dinitrile gave the corresponding methosulphate which was converted *in situ* into the methochloride. It was difficult to achieve satisfactory combustion analyses of this quaternary salt despite rigorous purification (cf. Barber *et al.*, *loc. cit.*). However, conversion into 2 : 7-diamidino-10-methyl-9-phenylphenanthridinium chloride dihydrochloride proceeded smoothly through the di-imino-ether.

p-Nitrobenzoyl chloride and 2-amino-4 : 4′-dibromodiphenyl in pyridine gave 4 : 4′-dibromo-2-*p*-nitrobenzamidodiphenyl in excellent yield, and very smooth ring closure to 2 : 7-dibromo-9-*p*-nitrophenylphenanthridine was accomplished by phosphorus oxychloride in nitrobenzene. Quaternation with methyl sulphate proceeded normally, the product being conveniently isolated as the hydrogen sulphate.

2 : 7-Dichloro-10-methyl-9-*p*-nitrophenylphenanthridinium methosulphate was obtained by a similar sequence of reactions and was reduced with iron and acetic acid to the corresponding amine, 9-*p*-aminophenyl-2 : 7-dichloro-10-methylphenanthridium chloride.

EXPERIMENTAL.

2 : 7-*Dicyano-9-phenylphenanthridine* [with Mrs. P. Z. SLACK, *née* Gregory].—2 : 7-Diamino-9-phenylphenanthridine (8·0 g.) in concentrated hydrochloric acid (18 c.c.) and water (50 c.c.) was

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tetrazotised at 0° with sodium nitrite (4·2 g.) in a little water. After neutralisation (sodium carbonate), the dark solution was poured, with stirring, into a solution of potassium cyanide (9·5 g.) and cuprous cyanide (6·3 g.) in water (25 c.c.). After being heated at 100° for 2 hours, the crude product was collected and washed with hot potassium cyanide solution, followed by boiling water. Sublimation at 0·1 mm./300° gave the yellow crystalline *dinitrile* (1·8 g.), m. p. 302° after recrystallisation from pyridine or anisole (Found : C, 82·9; H, 3·9; N, 13·5. $C_{21}H_{11}N_3$ requires C, 82·7; H, 3·6; N, 13·8%).

2 : 7-*Diamidino*-9-*phenylphenanthridine Dihydrochloride*.—The above dinitrile (0·75 g.) in absolute alcohol (15 c.c.) was saturated with dry hydrogen chloride at 0°, and the tube sealed and kept at room temperature for 3 weeks. The solid was collected, washed with dry ether, and treated with saturated alcoholic ammonia solution (25 c.c.) at 40—50° for 36 hours. After filtration, the solution was cooled very slowly, the *diamidine dihydrochloride* separating over a long period in beautiful pale-green rosettes. Recrystallisation from alcohol–ether (ice-box) gave the *monoalcoholate* (0·25 g.), m. p. (decomp.) 265—267° (Found : N, 15·8; Cl, 15·6; $C_{21}H_{19}N_5Cl_2,C_2H_5{\cdot}OH$ requires N, 15·35; Cl, 15·6%).

2 : 7-*Dicyano*-10-*methyl*-9-*phenylphenanthridinium Chloride*.—2 : 7-Dicyano-9-phenylphenanthridine (5·9 g.), dry nitrobenzene (50 c.c.), and methyl sulphate (4 c.c.) were gently refluxed for 5 minutes. The dark solution was cooled and shaken with ether (100 c.c.) and water (60 c.c.). The aqueous layer was separated and evaporated to half its volume. Ammonium chloride was added, and the precipitated *chloride* was crystallised from a little water, forming reddish needles, m. p. (decomp.) 300° (39%) (Found : N, 10·8; Cl, 10·9. $C_{22}H_{14}N_3Cl$ requires N, 11·8; Cl, 10·0%).

2 : 7-*Diamidino*-10-*methyl*-9-*phenylphenanthridinium Chloride Dihydrochloride*.—The above nitrile (510 mg.) was suspended in dry ethanol (10 c.c.) and saturated at 0° with dry hydrogen chloride. The mixture was kept for 2 days and diluted with dry ether. The precipitate was washed with dry ether and redissolved in saturated alcoholic ammonia (25 c.c.). After 15 hours at room temperature the solution was warmed to 40—50° for 1½ hours and evaporated to dryness at this temperature *in vacuo*. The residue was dissolved in water (5 c.c.) containing a little hydrochloric acid and reprecipitated by dropwise addition of acetone (30 c.c.). The high-melting *salt* (69%) formed needles from 4N-hydrochloric acid (Found : N, 12·6; Cl, 19·7. $C_{22}H_{22}N_5Cl_3,5H_2O$ requires N, 12·7; Cl, 19·3%).

2-*Amino*-4 : 4′-*dibromodiphenyl*.—This was prepared in 63% yield from the nitro-compound by Ritchie (*J. Proc. Roy. Soc. N.S.W.*, 1945, **78**, 141) by use of stannous chloride in ethanol. The following procedure was found more convenient. 4 : 4′-Dibromo-2-nitrodiphenyl (35·7 g.) was dissolved in boiling acetic acid (90 c.c.) and water (10 c.c.). Reduced iron powder (30 g.) was added at such a rate (during about 20 minutes) as to keep the mixture boiling vigorously; 80% acetic acid (40 c.c.) was added to replace evaporation losses. The mixture was heated for 30 minutes on the steam-bath, diluted with water (500 c.c.), and filtered. The solid was washed well with water and extracted with ether. The solution was dried and evaporated, giving a nearly colourless product (99%), m. p. 120°. This was pure enough for the next stage, but could be recrystallised from methanol to give pure material, m. p. 130°.

4 : 4′-*Dibromo*-2-p-*nitrobenzamidodiphenyl*.—A mixture of the above amine (3·27 g.), *p*-nitrobenzoyl chloride (2·0 g.), and dry pyridine (5 c.c.) was warmed for 75 minutes on the steam-bath and poured into 2N-hydrochloric acid (50 c.c.). The dark oil readily solidified and was washed with water and alcohol. The *benzoyl* compound (95%) crystallised from nitromethane as bright yellow needles, m. p. 203° (Found : N, 6·2; Br, 33·6. $C_{19}H_{12}O_3N_2Br_2$ requires N, 5·9; Br, 33·6%).

2 : 7-*Dibromo*-9-p-*nitrophenylphenanthridine*.—The above amide (2·8 g.), nitrobenzene (9 c.c.), and phosphorus oxychloride (4·5 c.c.) were refluxed for 6 hours in an oil-bath at 185°. The mixture was cooled, decomposed with ice, cautiously basified with concentrated aqueous ammonia, and steam-distilled. The residual solid was collected, and washed with water, alcohol, and ether. The *phenanthridine* (97%) formed khaki-coloured needles, m. p. 255°, from nitroethane (Found : N, 6·2; Br, 33·6. $C_{19}H_{10}O_2N_2Br_2$ requires N, 6·1; Br, 34·9%).

2 : 7-*Dibromo*-10-*methyl*-9-p-*nitrophenylphenanthridinium Hydrogen Sulphate*.—The above phenanthridine (1 g.) was heated for 15 minutes with gently refluxing nitrobenzene (10 c.c.) and methyl sulphate (0·5 c.c.). The solution was steam-distilled until all nitrobenzene had been removed, and the hot aqueous solution was decanted from tar. The yellow solid obtained after cooling was recrystallised from dilute sulphuric acid to give the *hydrogen sulphate* (33%), m. p. 226° (Found : N, 4·9; Br, 28·5. $C_{20}H_{12}O_2N_2Br_2,H_2SO_4$ requires N, 4·9; Br, 28·1%).

2-Amino-4 : 4′-dichlorodiphenyl is described by Monsanto and Jenkins (U.S.P. 2,084,033/1936), who reduced the nitro-compound with iron and hydrochloric acid. Using the method described for the bromo-analogue (above) we obtained an 84% yield of material having m. p. 91°. 4 : 4′-*Dichloro*-2-p-*nitrobenzamidodiphenyl*, prepared in 85% yield by the method described for the bromo-compound, crystallised from nitromethane in yellow needles, m. p. 203° (Found : N, 7·5. $C_{19}H_{12}O_3N_2Cl_2$ requires N, 7·2%).

2 : 7-*Dichloro*-9-p-*nitrophenylphenanthridine*.—The amide was cyclised as in the case of the bromo-phenanthridine, rather longer heating being required. The *phenanthridine*, which crystallised from nitromethane in pale yellow fluffy needles, m. p. 250°, was obtained in 70% yield, a small amount of unchanged amide being recovered (Found : N, 7·6; Cl, 19·0. $C_{19}H_{10}O_2N_2Cl_2$ requires N, 7·7; Cl, 19·2%).

2 : 7-*Dichloro*-10-*methyl*-9-p-*nitrophenylphenanthridinium Methosulphate*.—The phenanthridine (1 g.) was converted as above into the yellow *methosulphate* (92%), m. p. 320° (decomp.), after being washed with water, alcohol, and ether. It was insoluble in alcohol, water, acetic acid, nitrobenzene, and Cellosolve, and could not be further purified (Found : N, 5·7; Cl, 14·2. $C_{20}H_{12}O_2N_2Cl_2,CH_3{\cdot}HSO_4$ requires N, 5·7; Cl, 14·4%).

9-p-*Aminophenyl*-2 : 7-*dichloro*-10-*methylphenanthridinium Chloride*.—The nitro-compound (1 g.) and iron dust (1 g.) in 90% acetic acid (10 c.c.) were refluxed for 1 hour, after which the mixture was diluted with water and filtered. The filtrate was concentrated, treated with water, evaporated to low bulk, and redissolved in water (40 c.c.). This solution was then filtered and treated with ammonium chloride. The precipitated *chloride* was recrystallised from water, giving dull crimson prisms (95%), m. p. 216° (Found: C, 58·6; H, 4·6; N, 6·8; Cl, 24·9; 25·3. $C_{20}H_{15}N_2Cl_3,H_2O$ requires C, 58·9; H, 4·2; N, 6·9; Cl, 26·1%).

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