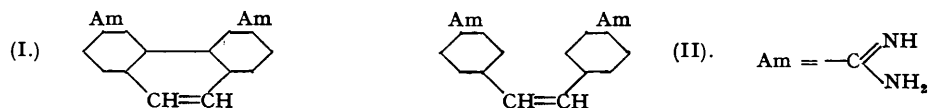


41. Phenanthrene-3:6-diamidine.

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A synthesis of phenanthrene-3:6-diamidine is described, and its trypanocidal action reported.

Phenanthrene-3:6-diamidine (I) is structurally related to *cis*-stilbene-4:4'-diamidine (II) (J., 1943, 2), which has a trypanocidal action similar to that of the *trans*-isomer ("Stilbamidine"). This diamidine has now been prepared and preliminary indications are that its trypanocidal activity is slight.



Phenanthrene-3:6-dinitrile, required for the preparation of the diamidine (I), has not been described, nor has the corresponding dinitro- or dibromo-phenanthrene, either of which would be a suitable intermediate. The literature on substitution in the phenanthrene (or hydrophenanthrene) series contra-indicated attempts at direct nitration or bromination and equally at introduction of other substituents readily convertible into nitrile groups, *e.g.*, $\text{NH}\cdot\text{C}\cdot\text{CCl}_2$, CH_2Cl , CHO . Since the conversion $\text{Br}\rightarrow\text{CN}$ by means of cuprous cyanide is generally preferable to the route $\text{NO}_2\rightarrow\text{NH}_2\rightarrow\text{CN}$, 3:6-dibromophenanthrene was selected as the intermediate to be obtained by the Pschorr method.

4-Bromo-2-nitrobenzaldehyde has been prepared by oxidation of 4-bromo-2-nitrotoluene by amyl nitrite (Rottig, *J. pr. Chem.*, 1935, 142, 35). 4-Bromo-2-nitrotoluene was prepared by nitration of *p*-toluidine sulphate (Ullmann and Dootson, *Ber.*, 1918, 51, 9), followed by a Sandmeyer reaction. Attempts to repeat the oxidation with amyl nitrite gave very low yields; manganese dioxide, *p*-nitrosodimethylaniline and bromine were tried without success, but reaction with chromic acid in acetic acid-anhydride was a workable method, although the yield was only 17–18%.

The Perkin condensation, reduction, and Pschorr ring-closure presented no difficulties, but the 3:6-dibromophenanthrene-9-carboxylic acid could not readily be purified. Attempts to decarboxylate the crude acid by repeated sublimation or by the action of copper chromite in quinoline gave poor results. Simultaneous conversion into dinitrile and loss of carbon dioxide occurred when the sublimed acid was heated with cuprous cyanide in boiling quinoline.

The iminoether hydrochloride was prepared in chloroform by the usual method, and the crude iminoether base isolated and converted directly into the amidine isethionate. As this salt was too soluble for convenient isolation, the hydrochloride was precipitated, and crystallised from hydrochloric acid.

Toxicity and trypanocidal tests (*T. equiperdum* in mice) gave the following results:

	L.D. ₅₀	E.D. ₅₀	C.D. ₅₀	Chemotherapeutic index.
Intravenous injection	0.03 mg./g.	0.0075 mg./g.	—	—
Subcutaneous injection	0.14 mg./g.	0.005 mg./g.	0.05 mg./g.	3

(E.D.₅₀: mean effective dose—trypanosomes cleared from peripheral blood after 3 days.

C.D.₅₀: mean curative dose—trypanosomes cleared from peripheral blood for 28 days or longer.)

EXPERIMENTAL.

All analyses are semi-micro.

4-Bromo-2-nitrobenzylidene Diacetate.—4-Bromo-2-nitrotoluene (20 g.; 0.087 g.-mol.) was dissolved in glacial acetic acid (40 c.c.) and acetic anhydride (220 c.c.), and sulphuric acid (21 c.c.; 0.25 g.-mol.) added with stirring. The whole was cooled to 5°, and a solution of chromium trioxide (25 g.; 0.25 g.-mol.) in water (15 c.c.) and glacial acetic acid (100 c.c.) added during 30 minutes at 5–10°. The mixture was stirred for a further 30 minutes, then poured into ice-water (1.5 l.). The product was collected, washed until the filtrate was colourless, and dried in a vacuum; yield, 12 g. The diacetate, after crystallising from alcohol, then twice from methanol, gave white rhombs, m. p. 133–136° (Found: Br, 24.0. C₁₁H₁₀O₆NBr requires Br, 24.1%).

4-Bromo-2-nitrobenzaldehyde.—Crude 4-bromo-2-nitrobenzylidene diacetate (12 g.) was boiled for 1½ hours with alcohol (100 c.c.) and 2*N*-sulphuric acid (100 c.c.). The solution, after cooling, was treated with water (350 c.c.). The aldehyde was extracted with ether, and the extract washed with water, evaporated to 100 c.c., shaken with saturated sodium bisulphite solution (50 c.c.), and kept overnight. The bisulphite compound was collected, washed with ether, dissolved in warm water (60 c.c.), and decomposed with 2*N*-sodium carbonate (100 c.c.). The aldehyde was collected, washed with water, and dried in a vacuum; light yellow solid, m. p. 95–97°; yield, 3.7 g. (17.5%, based on the 4-bromo-2-nitrotoluene used).

Sodium 4-Bromophenylacetate.—4-Bromophenylacetonitrile (prepared from 4-bromobenzyl bromide by the method of Wislicenus and Elvert, *Ber.*, 1908, 41, 4121) was hydrolysed in 50% sulphuric acid in the usual way, and converted into the sodium salt.

cis-4:4'-Dibromo-2'-nitrostilbene- α -carboxylic Acid.—4-Bromo-2-nitrobenzaldehyde (6.9 g.; 0.03 g.-mol.), sodium 4-bromophenylacetate (7.2 g.; 0.03 g.-mol.), and acetic anhydride (50 c.c.) were heated together at 105–115° for 22 hours with occasional shaking. The excess of acetic anhydride was decomposed with water at 100–120°, and water then added. After cooling, the liquid was decanted, and the sticky residue dissolved in ether and washed with water. On extraction of the ethereal solution with 2*N*-aqueous ammonia, three layers were obtained, the lowest one solidifying on long standing, and the two lower layers forming a single one on warming (the lowest layer was probably the sparingly soluble ammonium salt). The ammoniacal extract was warmed for complete solution, and poured into dilute hydrochloric acid. The crude orange solid thus obtained was collected and washed with water; m. p. 180–190°. On crystallisation from glacial acetic acid (130 c.c.)–water (25 c.c.) the acid was obtained as orange rods, m. p. 204–206°; yield, 12.8 g. (52%) (Found: Br, 37.4; N, 3.3. C₁₅H₉O₄NBr₂ requires Br, 37.4; N, 3.3%).

cis-4:4'-Dibromo-2'-aminostilbene- α -carboxylic Acid.—Ferrous sulphate (FeSO₄·7H₂O) (12.5 g.; 0.045 g.-mol.) was dissolved in water (50 c.c.) on the steam-bath, and a mixture of aqueous ammonia (*d* 0.880) (25 c.c.) and water (25 c.c.) added. To the hot suspension of ferrous hydroxide was added immediately a solution of *cis*-4:4'-dibromo-2'-nitrostilbene- α -carboxylic acid (2.13 g.; 0.005 g.-mol.) in warm 2*N*-aqueous ammonia (10 c.c.). After heating for 1½ hours on the steam-bath, the mixture was filtered hot, with the aid of charcoal and kieselguhr. The residue was repeatedly extracted with boiling dilute aqueous ammonia, until no precipitate was produced on acidification of the filtrate with acetic acid (about four extractions); in some cases it was necessary to refilter with charcoal to remove colour and iron. The combined extracts were warmed (to dissolve crystals of the ammonium salt) and made acid to litmus with acetic acid. The acid came down as a bright yellow solid but rapidly turned white on shaking for a few minutes. After cooling, the crude material was filtered, washed with water and dried in a vacuum; m. p. 188–191°; yield, 1.75 g. (87%). Recrystallisation from 65% alcohol (25 vols.) (charcoal) gave the acid as brownish-white narrow plates, m. p. 192–194°; yield, 1.55 g. (78%) (Found: Br, 40.1. C₁₅H₁₁O₄NBr₂ requires Br, 40.3%).

3:6-Dibromophenanthrene-9-carboxylic Acid.—*cis*-4:4'-Dibromo-2'-aminostilbene- α -carboxylic acid (1.0 g.; 0.0025 g.-mol.) was suspended in alcohol (15 c.c.), and sulphuric acid (0.3 c.c.; 0.0055 g.-mol.) added with shaking. After a few minutes the sulphate crystallised. The thick paste was stirred and cooled to room temperature, and amyl nitrite (0.6 c.c.; 0.0045 g.-mol.) added all at once with stirring. The practically clear solution after a few minutes began to deposit feathery yellow crystals. After an hour these changed to a fine heavy yellow powder (in one experiment this change did not occur).

Calcium hypophosphite (4.25 g.; 0.25 g.-mol.) in hot water (35 c.c.) was stirred with sodium carbonate (3.2 g. of monohydrate; 0.26 g.-mol.) in hot water (25 c.c.), a trace of copper bronze added to the filtered solution, and the temperature adjusted to about 50°. The suspension of diazonium salt was poured in during 2 minutes with stirring, and the mixture heated for 15 minutes on the steam-bath. The brown solid was collected, washed with water, and dried in the oven. The crude acid was thus obtained as a brown powder; yield, 0.85 g. (88%). In a number of experiments the

yield varied from 70 to 90%. For analysis, a small quantity was crystallised from chlorobenzene, the *acid* being obtained as a brown powder, m. p. 290—292° (Found: Br, 42.3. $C_{15}H_8O_2Br_2$ requires Br, 42.1%).

3 : 6-Dibromophenanthrene.—(A) Crude 3 : 6-dibromophenanthrene-9-carboxylic acid (0.85 g.) was dissolved in ether (500 c.c.) and filtered from copper, and the ether evaporated. The residue was sublimed at 250°/1 mm., giving a yellowish-white sublimate, m. p. 260° upwards. This was resublimed, m. p. about 280°, with sintering. The product was largely soluble in alkali; yield, 0.35 g.

(B) The sublimed material was added to quinoline (5 c.c.) at 210—220°, containing copper chromite catalyst. After heating for 10 minutes, the solution was cooled somewhat and poured into concentrated hydrochloric acid (50 c.c.), boiled, filtered, washed with water, and dried at 90°. The black powder was sublimed at 180—190°/1 mm., and the white sublimate crystallised from petrol, from which there separated white needles, m. p. 188—191°.

A repetition of this experiment, using unsublimed acid, gave a low yield of less pure *material*, m. p. 183—188° (Found: Br, 47.2. $C_{14}H_8Br_2$ requires Br, 47.6%).

Phenanthrene-3 : 6-dinitrile.—Crude 3 : 6-dibromophenanthrene-9-carboxylic acid (4.4 g.) was sublimed at 260—290°/1 mm., the yellowish-white sublimate (1.85 g.) mixed with cuprous cyanide (1.14 g.) and added to boiling quinoline (6 c.c.) during 5 minutes, and the solution boiled for a further 30 minutes. After cooling somewhat, the mixture was poured into concentrated hydrochloric acid (100 c.c.), boiled, filtered, washed with more acid, and then with water. The grey solid was washed with cold sodium hydroxide solution (to remove unchanged acid and phenolic compounds), and then with water, and dried at 90°. The crude material was sublimed at 220—230°/0.6 mm., to give fine, slightly yellow needles; 0.55 g. (50%) (overall yield from amine, 16—17%). Recrystallisation from glacial acetic acid (60 vols.) gave a 76% return of the *nitrile* as long white needles, m. p. 257—259° (Found: N, 12.15. $C_{16}H_8N_2$ requires N, 12.3%).

The preparation was also tried with unsublimed acid, but yields were lower still; in one case no nitrile was isolated.

Phenanthrene-3 : 6-diamidine.—The method described in B.P. 559,015 was used. The *dihydrochloride* crystallised from dilute hydrochloric acid in white needles; yield, 41% (Found: N, 14.6; Cl, 18.15. $C_{16}H_{14}N_4 \cdot 2HCl \cdot 3H_2O$ requires N, 14.4; Cl, 18.25%).

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