2. *Phenanthridines. Part I. The Synthesis of Bromophenanthridines.*

By G. M. Badger and W. F. H. Sasse.

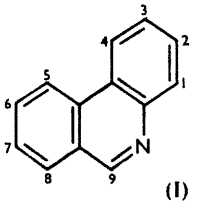
2-, 3-, and 7-Bromophenanthridine have been prepared by cyclisation of the bromo-2-formamidodiphenyls with polyphosphoric acid. Attempts to cyclodehydrate 2-formamido-2′-nitro- and 2 : 2′-diformamido-diphenyl by this reagent were unsuccessful; but treatment of the latter diphenyl with aluminium chloride–sodium chloride above 250° gave 4 : 9-diazapyrene.

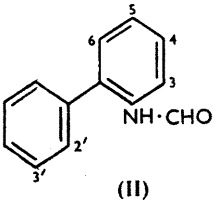
Although the chemistry of phenanthridine (I) has been attracting increasing interest in recent years, little work has been done on the properties of the parent base.[1] With its nine non-equivalent positions available for substitution, phenanthridine is extremely useful for the comparison of substitution orientations with theoretical calculations.[2] Bromination of phenanthridine was selected for study, and as a preliminary step the synthesis of the nine monobromophenanthridines was undertaken. However, Gilman and Eisch [3] have recently shown that bromination with *N*-bromosuccinimide gives 3-bromophenanthridine as the major product, and this prompted us to record our synthetic work at this stage. 9-Bromophenanthridine is well known [4] and the present paper records the synthesis of 2-, 3-, and 7-bromophenanthridine, as well as some unsuccessful attempts to obtain 5-bromophenanthridine.

A useful method for the synthesis of 9-substituted phenanthridines—cyclisation of 2-acylaminodiphenyls with phosphoryl chloride under relatively mild conditions [5]—fails with 2-formamidodiphenyl (II). Ockenden and Schofield [6] used a mixture of phosphoryl chloride, stannic chloride, and nitrobenzene with success, and Taylor and Kalenda [7]

[1] For a review see Walls in Elderfield's "Heterocyclic Compounds," Wiley, New York, 1952, Vol. IV.
[2] Longuet-Higgins and Coulson, *J.*, 1949, 971.
[3] Gilman and Eisch, *J. Amer. Chem. Soc.*, 1955, **77**, 6379.
[4] Walls, *J.*, 1934, 104.
[5] Morgan and Walls, *J.*, 1931, 2447.
[6] Ockenden and Schofield, *J.*, 1953, 717.
[7] Taylor and Kalenda, *J. Amer. Chem. Soc.*, 1954, **76**, 1699.

prepared phenanthridine in excellent yield by cyclisation of 2-formamidodiphenyl with polyphosphoric acid.[8] This use of polyphosphoric acid was developed independently by the present authors: 5-bromo-2-formamidodiphenyl readily gave 3-bromophenanthridine in good yield on use of polyphosphoric acid equivalent to $\leqslant 84\%$ of phosphorus pentoxide in water,[9] but with less concentrated acid no cyclisation occurred.


(I)



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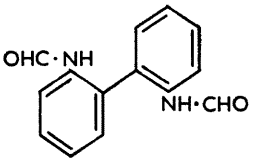

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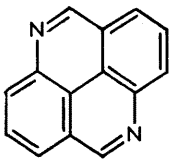
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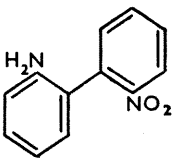

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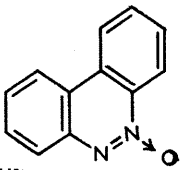
(VI)

The cyclisation of 4-bromo- and 4′-bromo-2-formamidodiphenyl likewise smoothly yielded 2- and 7-bromophenanthridine respectively; but great difficulty was experienced with 2′-substituted 2-formamidodiphenyls. Attempts to cyclise 2-formamido-2′-nitrodiphenyl were unavailing, and it is of interest that Arcus and Coombs [10] were unable to cyclise 2-formamido-4′-nitrodiphenyl by the phosphoryl chloride–stannic chloride method. Attempts to cyclise 2 : 2′-diformamidodiphenyl (III) with polyphosphoric acid were also unsuccessful, only 2 : 2′-diaminodiphenyl being recovered. The same compound was also recovered when fused sodium chloride–aluminium chloride was used at $<250°$, but at somewhat higher temperatures cyclisation did occur to give a substance which is regarded as 4 : 9-diazapyrene (IV; Ring Index numbering).

These results support the view [11] that the cyclisation of acylaminodiphenyls involves the formation of a carbonium ion, and that the subsequent reaction can be considered as an intramolecular electrophilic substitution. With the formamidodiphenyls (II), however, the absence of the alkyl group increases the difficulty of forming the carbonium ion and much more vigorous experimental conditions (*e.g.*, polyphosphoric acid) are required. The presence of deactivating substituents (NO_2, NH·CHO) again decreases the reactivity, and cyclisation of 2-formamido-2′-nitro- and of 2 : 2′-diformamido-diphenyl could not be effected with polyphosphoric acid.

Several methods have been used for the preparation of the intermediate 2-formamidodiphenyls. 2-Amino-5-bromodiphenyl was prepared by bromination of 2-acetamidodiphenyl followed by hydrolysis, according to the method of Scarborough and Waters,[12] and formylation was effected with formic acid. The mother-liquors from the bromination contained only traces of other isomers.

For the preparation of 4-bromo-2-formamidodiphenyl, 4-bromo-2-nitroaniline was diazotised and treated with benzene in the presence of sodium acetate, a procedure which proved better than the more usual Gomberg reaction involving the use of sodium hydroxide. The resulting 4-bromo-2-nitrodiphenyl was reduced with stannous chloride and the crude amine formylated.

By a modified Sandmeyer reaction, 4-amino-2′-nitrodiphenyl was converted into 4-bromo-2′-nitrodiphenyl, which was reduced with stannous chloride and then formylated

[8] See also Snyder and Werber, *J. Amer. Chem. Soc.*, 1950, **72**, 2962.
[9] Bell, *Ind. Eng. Chem.*, 1948, **40**, 1464.
[10] Arcus and Coombs, *J.*, 1954, 4319.
[11] Ritchie, *Proc. Roy. Soc. N.S.W.*, 1944, **78**, 147.
[12] Scarborough and Waters, *J.*, 1927, 89.

to give 4-bromo-2-formamidodiphenyl, but this method proved somewhat tedious on a larger scale. Direct bromination of 2-nitrodiphenyl was accordingly investigated, and it was hoped also that this would furnish other bromonitrodiphenyls. The crude bromination product was reduced with stannous chloride and fractionated. 2-Amino-4'-bromodiphenyl was readily isolated (as the formyl derivative) in useful amount, but the only other product which could be obtained was 4-amino-4'-bromodiphenyl. The latter compound was presumably formed from some 4-nitrodiphenyl present as an impurity in the commercial 2-nitrodiphenyl used for the bromination.

Several attempts were made to prepare suitable intermediates for the synthesis of 5-bromophenanthridine. 2-Amino-2'-nitrodiphenyl (V) was prepared by partial reduction of 2 : 2'-dinitrodiphenyl, some 3 : 4-benzocinnoline *N*-oxide (VI) being also obtained. However, 2-formamido-2'-nitrodiphenyl could not be cyclised. Similarly, 2 : 2'-diaminodiphenyl [13] was formylated, and this also failed to give a phenanthridine. In a further attempt, it was hoped to prepare 2-bromo-2'-formamidodiphenyl, but attempts to obtain the intermediate 2-bromo-2'-nitrodiphenyl in quantity from 2-amino-2'-nitrodiphenyl had so little success that the method was abandoned.

Experimental

3-Bromophenanthridine.— (a) *5-Bromo-2-formamidodiphenyl.* 2-Amino-5-bromodiphenyl [12] was heated on the steam-bath with excess of 98—100% formic acid for 6 hr. After removal of the excess of acid *in vacuo*, *5-bromo-2-formamidodiphenyl* recrystallised from ethanol as needles, m. p. 105° (Found: C, 56·5; H, 3·85; Br, 28·6. $C_{13}H_{10}ONBr$ requires C, 56·5; H, 3·65; Br, 28·6%).

(b) *3-Bromophenanthridine.* Syrupy phosphoric acid (18 c.c.; 85% of orthophosphoric acid) was heated to 180° and phosphoric oxide (38 g.) added in small portions *without* stirring. (Continuous stirring at this stage leads to the formation of lumps which do not dissolve at 200°.) The mixture was then gently stirred for 1—2 min. After a further 15 min., gentle stirring was resumed, and approx. 90% of the oxide had dissolved after 50 min. The mixture was cooled to 150° and 5-bromo-2-formamidodiphenyl (2·0 g.) added with stirring. The whole of the pentoxide dissolved at this stage and the mixture was heated at 150°, with stirring, for a further 2 hr., then poured into water and basified with ammonia, and the solid collected. 3-Bromophenanthridine (1·6 g., 85%) crystallised from ethanol as needles, m. p. 161·5—162·5° (Found: C, 60·4; H, 3·1; Br, 31·0. Calc. for $C_{13}H_8NBr$: C, 60·5; H, 3·1; Br, 31·0%). Gilman and Eisch [3] give m. p. 162·0—163·0° (corr.).

In experiments with weaker polyphosphoric acid (*e.g.*, 20 g. of phosphoric oxide and 20 c.c. of syrupy phosphoric acid), the sole product was 2-amino-5-bromodiphenyl, m. p. and mixed m. p. 56—57°.

2-Bromophenanthridine.—(a) *4-Bromo-2-nitroaniline.* Bromine (118 g.) in acetic acid (200 c.c.) was added, with stirring, to an ice-cooled solution of *o*-nitroaniline (100 g.) and crystallised sodium acetate (100 g.) in acetic acid (1 l.). Then the mixture was kept at room temperature for 1 hr., and poured into water (8 l.). After three recrystallisations from ethanol the 4-bromo-2-nitroaniline (135 g.) had m. p. 109—110° (lit., 111—112°).

(b) *4-Bromo-2-nitrodiphenyl.* The solution obtained from 4-bromo-2-nitroaniline (40 g.) in concentrated hydrochloric acid (250 c.c.), water (250 c.c.), and acetic acid (100 c.c.) was diazotised at 5° in the usual way. After filtration, benzene (500 c.c.) and crystallised sodium acetate (250 g.) were added to the vigorously stirred solution, at 5—10°. Stirring was continued for 45 hr. at room temperature. The organic layer was then separated and stirring continued with a further quantity (300 c.c.) of benzene for 3 hr. The process was repeated with 200 c.c. of benzene, and the combined benzene extracts were dried ($CaSO_4$), concentrated to 100 c.c., and passed through a column of alumina, which was eluted with light petroleum (b. p. 40—100°). The crude diphenyl (22 g.) obtained by evaporation of the first 4 l. of eluate had b. p. 120—150°/0·6 mm. and was redistilled (b. p. 123°/0·05 mm.; 18 g., 28%) before recrystallisation from light petroleum (b. p. 60—80°). *4-Bromo-2-nitrodiphenyl* formed pale yellow needles, m. p. 59—60° (Found: C, 52·15; H, 3·0; Br, 28·4. $C_{12}H_8O_2NBr$ requires C, 51·8; H, 2·9; Br, 28·7%).

Experiments in which sodium hydroxide replaced sodium acetate gave more tar and only 10% of product.

(c) *4-Bromo-2-formamidodiphenyl.* A solution of 4-bromo-2-nitrodiphenyl (20 g.) in ethanol

[13] Stephenson, *J.*, 1954, 2354.

(50 c.c.) was added to a hot solution of stannous chloride (50 g.) in concentrated hydrochloric acid (50 c.c.) and ethanol (50 c.c.). After 1 hour's refluxing the mixture was basified, cooled, and extracted with ether. Distillation through a column (2 × 20 cm.) filled with single-turn glass helices yielded the crude amine (17 g.; b. p. 156°/2 mm.) which was formylated with formic acid. *4-Bromo-2-formamidodiphenyl* separated from benzene–light petroleum (b. p. 60—80°) as long needles, m. p. 107·5—108·5° (Found: C, 56·9; H, 3·65; Br, 28·6. $C_{13}H_{10}ONBr$ requires C, 56·5; H, 3·65; Br, 28·9%).

(d) *2-Bromophenanthridine.* Cyclisation of 4-bromo-2-formamidodiphenyl, as for the 3-bromo-derivative, gave 2-bromophenanthridine (85%) as needles, m. p. 122—123°, from benzene or ethanol (Found: C, 60·9; H, 3·2; Br, 30·7. $C_{13}H_8NBr$ requires C, 60·5; H, 3·1; Br, 31·0%).

7-Bromophenanthridine.—(a) *4-Bromo-2′-nitrodiphenyl.* A solution of 4-amino-2′-nitrodiphenyl [14] (4 g.) in water (800 c.c.) and 30% hydrobromic acid (40 c.c.) was diazotised at 0—5°. A solution of mercuric nitrate in saturated aqueous sodium bromide was then added until no more precipitate separated. After 10 min. at 5° the solid was collected and air-dried (9·25 g.). The complex (which was stable at room temperature) was finely ground with sodium bromide (90 g.), and heated slowly in a flat-bottomed flask under an air condenser. Decomposition started at 140° (bath-temp.) and the mixture became black. The bath-temperature was then raised to 200° for 10 min. Extraction with boiling benzene (3 × 300 c.c.), chromatography on alumina, and elution with 2 l. of benzene–carbon tetrachloride (2 : 1) gave 4-bromo-2′-nitrodiphenyl (2·5 g.) as pale yellow plates, m. p. 65—66° (lit., 65°).

(b) *2-Amino-4′-bromodiphenyl.* 4-Bromo-2′-nitrodiphenyl was reduced with stannous chloride as described below for the mixed bromonitrodiphenyls. After distillation, *2-amino-4′-bromodiphenyl* (80% yield) had b. p. 112—114°/0·05 mm., m. p. 44—45° (Found: C, 58·2; H, 4·2; Br, 32·0. $C_{12}H_{10}NBr$ requires C, 58·1; H, 4·1; Br, 32·2%).

(c) *4-Bromo-2′-formamidodiphenyl.* The above base was formylated (in 95% yield) as above. *4-Bromo-2′-formamidodiphenyl* separated from ethanol as needles, m. p. 119—120° (Found: C, 56·7; H, 3·8; Br, 28·9. $C_{13}H_{10}ONBr$ requires C, 56·5; H, 3·65; Br, 28·9%). The *toluene-p-sulphonyl derivative* was obtained as needles, m. p. 130°, from ethanol and from benzene (Found: C, 56·8; H, 4·2; Br, 20·1. $C_{19}H_{16}O_2NBrS$ requires C, 56·7; H, 4·1; Br, 19·9%).

(d) *Bromination of 2-nitrodiphenyl.* Bromine (27·5 c.c.) was added as vapour (in nitrogen as carrier) to a mixture of commercial 2-nitrodiphenyl (100 g.) and iron powder (1 g.) at 135—155°, the rate of flow being adjusted to avoid loss of bromine. Uptake of bromine was complete after 8 hr. The crude product was dissolved in ethanol (200 c.c.), filtered, and added dropwise to stannous chloride (370 g.) in hot concentrated hydrochloric acid (400 c.c.), water (200 c.c.), and ethanol (200 c.c.). After the initial exothermic reaction refluxing was continued for 30 min. Sodium hydroxide (470 g.) in water (1 l.) was added and the bulk of the ethanol driven off by the heat of neutralisation. After cooling, the solution was extracted with ether, the extract dried ($CaSO_4$) and evaporated, and the product distilled, giving fractions: (i) b. p. 130—135°/1 mm. (11 g.), identified as 2-aminodiphenyl; (ii) b. p. 140—150°/1·2 mm. (3·5 g.); (iii) b. p. 150—168°/1·2 mm. (69 g.); and (iv) b. p. 168—188°/1·2 mm. (5 g.).

Fraction (iii), a pale green oil, was formylated, to yield a product, m. p. 105—110° (41 g.). After two recrystallisations from ethanol it formed needles (30 g.), m. p. 119—120° alone or mixed with 4-bromo-2′-formamidodiphenyl prepared as described above. The mother-liquors were separated into at least three different fractions, but these were not further investigated.

Fraction (iv) was combined with the residue from the distillation, and treated with boiling ethanol (250 c.c.). The residue (2·5 g.) was set aside [fraction (v)], but the solution deposited light brown crystals (14 g.). Distillation (b. p. 190°/3·5 mm.) and recrystallisation from benzene gave 4-amino-4′-bromodiphenyl (4·2 g.) as plates, m. p. 144·5—145° (Found: C, 58·0; H, 4·4; N, 5·4; Br, 32·3. Calc. for $C_{12}H_{10}NBr$: C, 58·1; H, 4·1; N, 5·7; Br, 32·2%) (lit., m. p. 145°). Formylation of this base gave *4-bromo-4′-formamidodiphenyl* as leaflets, m. p. 167—168° (Found: N, 4·8; Br, 28·8. $C_{13}H_{10}ONBr$ requires N, 5·1; Br, 28·9%).

The residue from the last distillation was combined with fraction (v), and purified by chromatography, followed by recrystallisation from xylene. The product, m. p. 296° (Found: Br, 74·4%), was not further examined.

(e) *7-Bromophenanthridine.* Cyclisation of 4-bromo-2-formamidodiphenyl was carried out in polyphosphoric acid as described for 3-bromophenanthridine. *7-Bromophenanthridine* was obtained (80%) as needles, m. p. 86—87°, from benzene–light petroleum (b. p. 60—80°) (Found: C, 60·5; H, 3·1; Br, 31·3. $C_{13}H_8NBr$ requires C, 60·5; H, 3·1; Br, 31·0%).

[14] Walls, *J.*, 1947, 67.

5-Bromophenanthridine.—(a) *2-Amino-2′-nitrodiphenyl.* The following method was superior to Purdie's.[15] 2 : 2′-Dinitrodiphenyl (50 g., 0·205 mole) in hot methanol (650 c.c.) was treated with sodium hydrogen sulphide [0·369 mole; from crystallised sodium sulphide (89 g.), sodium hydrogen carbonate (31 g.), water (220 c.c.), and methanol (220 c.c.), cf. Hodgson and Ward [16]], refluxed for 30 min., and kept overnight, water was added, methanol removed, and the oily residue dissolved in ether. The aqueous layer was extracted with ether and the combined ethereal solutions were repeatedly extracted with dilute hydrochloric acid. The acid extracts were basified and the product was re-extracted into ether. After removal of the ether the crude material was chromatographed in benzene on alumina (250 g.), to give 2-amino-2′-nitrodiphenyl (35 g., 80%), m. p. 63—65°. Repeated recrystallisation from benzene–light petroleum gave the pure product, m. p. (constant) 64·0—64·5°, but an analytical sample prepared by three sublimations at 80—85°/0·01 mm. had m. p. 71° (Found : C, 67·45; H, 4·95; N, 13·3. Calc. for $C_{12}H_{10}O_2N_2$: C, 67·3; H, 4·7; N, 13·1%). After recrystallisation from benzene–light petroleum the sublimed material again had m. p. 64·0—64·5°. A pure product having the same m. p. was also obtained by following the directions of Purdie [15] who, however, records m. p. 94—95°.

The ethereal solution remaining after extraction with acid was evaporated and chromatographed on alumina with benzene–carbon tetrachloride (1 : 1) as eluant. Recrystallisation from ethanol gave 3 : 4-benzocinnoline *N*-oxide (5·5 g.), m. p. 137—137·5° alone or mixed with an authentic specimen.[17]

(b) *2-Formamido-2′-nitrodiphenyl.* Formylation of the above aminonitrodiphenyl gave *2-formamido-2′-nitrodiphenyl* as pale yellow needles, m. p. 130—131° (from ethanol) (Found : C, 64·8; H, 4·3; N, 11·5. $C_{13}H_{10}O_3N_2$ requires C, 64·5; H, 4·2; N, 11·6%).

2 : 2′-Diformamidodiphenyl. 2 : 2′-Diaminodiphenyl [13] gave 2 : 2′-diformamidodiphenyl as colourless needles, m. p. 145—146°, from ethanol (Found : C, 70·3; H, 5·2; N, 12·0; O, 13·1. Calc. for $C_{14}H_{12}O_2N_2$: C, 70·0; H, 5·0; N, 11·7; O, 13·3%) (lit., m. p. 137°).

(c) *4 : 9-Diazapyrene.* 2 : 2′-Diformamidodiphenyl (3 g.), aluminium chloride (53 g.), and sodium chloride (11 g.) were heated at 250—280° for 8 hr. After decomposition with water, the mixture was basified and filtered. Purification by chromatography in benzene on a short column of alumina, and recrystallisation from ethanol, gave *4 : 9-diazapyrene* (2·16 g., 85%) as light brown needles, m. p. 209—210° (darkening from 200°) (Found : C, 82·3; H, 3·6; N, 14·0. $C_{14}H_8N_2$ requires C, 82·3; H, 3·9; N, 13·7%). Its ultraviolet absorption spectrum, in 95° ethanol, was similar to that of pyrene [18] except that the group III bands were more intense.[19] Maxima (mμ) and log ε values were as follows : 236 (4·85); 256 (4·32); 268 (4·40); 305 (4·12); 318 (4·18); 330 (4·24); 344 (3·77); 352 (3·82); 362 (3·63); 370 (4·02).

(d) *2-Bromo-2′-nitrodiphenyl.* The following method was superior to Mascarelli and Gatta's.[20] Bromine (6 g.) in acetic acid (60 c.c.) was added, with ice-cooling and stirring, to a diazotised solution of 2-amino-2′-nitrodiphenyl (6 g.) in 30% hydrobromic acid (30 c.c.) and water (150 c.c.). The red oily precipitate was isolated by decantation, washed with ice-cold water, and decomposed by gentle heating in ethanol (300 c.c.) and acetic acid (50 c.c.). Pouring into water gave a crude product which was chromatographed on alumina in benzene, benzene–carbon tetrachloride (1 : 1) being used as eluant. Recrystallisation from benzene–light petroleum gave 2-bromo-2′-nitrodiphenyl (720 mg.) as pale yellow rods, m. p. 70—71° (Found : C, 52·2; H, 3·2; Br, 29·0. Calc. for $C_{12}H_8O_2NBr$: C, 51·8; H, 2·9; Br, 28·8%). Mascarelli and Gatta [20] give m. p. 66—67°.

Other solvents (including acetic acid, ethanol, acetone, and methanol–acetone) for the decomposition of the diazonium perbromide were less satisfactory, as were attempts to prepare this compound by the Sandmeyer reaction with or without the isolation of the diazonium compound.

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