Tetrahedron, 1963, Vol. 19, pp. 1841 to 1848. Pergamon Press Ltd. Printed in Northern Ireland

PHENAZINES—III

THE SYNTHESIS OF 7-AMINOPHENAZINE-1-, 7-AMINOPHENAZINE-2- AND 8-AMINOPHENAZINE-2-CARBOXYLIC ACIDS*

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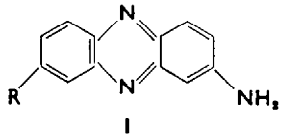
(*Received* 22 *July* 1963)

Abstract—Ferric chloride oxidation of 2,4′-diamino-4- and -5-cyanodiphenylamines led to 2-amino-8- and -7-cyanophenazines respectively which could be hydrolysed to the corresponding 7- and 8-aminophenazine-2-carboxylic acids. 8-Aminophenazine-2-carboxylic acid was also made by the oxidative cyclization in boiling nitrobenzene of 2,4′-diaminodiphenylamine-4-carboxylic acid; 4′,6-diaminodiphenylamine-2-carboxylic acid similarly gave 7-aminophenazine-1-carboxylic acid.

A RED, crystalline pigment from *Pseudomonas aeruginosa* appeared to be the internal salt of a 2-amino-?-carboxy-10-methylphenazinium hydroxide,[1] the action of alkali producing the parent 2-aminophenazine carboxylic acid.[2] Lack of material prevented further degradative work to establish the position of the carboxyl group and physical methods gave little promise of success, particularly in the absence of a range of suitable reference compounds. A programme aimed at the synthesis of the seven possible 2-aminophenazine carboxylic acids was therefore instituted.

At the time of commencement of this programme, no aminophenazine carboxylic acid had been reported, although recently the synthesis of 1-aminophenazine-2-carboxylic acid has been described.[3] We sought an approach which would be generally applicable to the whole series. The most attractive route appeared to be in the direct synthesis of 2-aminophenazines by the oxidative cyclization of 2,4′-diaminodiphenylamines,[4,5] and, in the first instance, we selected 8-aminophenazine-2-carboxylic acid (I, R = CO_2H) as the immediate goal.



I

IIa, R = CN, R′ = NO_2, R″ = H.
IIb, R = CN, R′ = NH_2, R″ = H.
IIc, R = CO_2H, R′ = NO_2, R″ = H.
IId, R = CO_2H, R′ = NH_2, R″ = H.
IIe, R = CN, R′ = NO_2, R″ = Ac.
IIf, R = CO_2H, R′ = NO_2, R″ = Ac.

* The numbering system used is that with the nitrogen atoms numbered 5 and 10.

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[1] F. G. Holliman, *Chem. & Ind.* 1668 (1957).
[2] F. G. Holliman, *South African Ind. Chem.* **15**, 233 (1961).
[3] J. H. Boyer and L. R. Morgan, *J. Org. Chem.* **26**, 1654 (1961).
[4] A. Gray, G. Gaertner and F. G. Holliman, *Tetrahedron Letters* No. 7, 24 (1959).
[5] G. Gaertner, A. Gray and F. G. Holliman, *Tetrahedron* **18**, 1105 (1962).

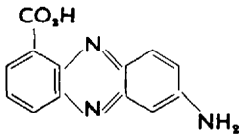
2,4′-Diamino-4-cyanodiphenylamine (IIb), required for the synthesis of 2-amino-8-cyanophenazine (I, R = CN), was prepared by three routes, the most suitable being the catalytic hydrogenation of 4-amino-4′-cyano-2′-nitrodiphenylamine[6] (IIa). Oxidative cyclization in boiling nitrobenzene of the diaminodiphenylamine gave indications that the formation of 2-amino-8-cyanophenazine (I,R = CN) took place, although very slowly. (Subsequent investigations[7] have shown that the 4-cyano group retards the reaction.) We therefore investigated other oxidizing agents and found that the addition of ferric chloride to a hot, acid solution of the diaminodiphenylamine gave a quantitative yield of the hydrochloride of the required phenazine. Although acid hydrolysis of the cyanophenazine appeared to be successful, isolation of the product proved difficult; alkaline hydrolysis gave an amphoteric product which had the properties expected for a 2-aminophenazine carboxylic acid. It was not crystalline, however, and resisted all attempts at purification.

An attempt was now made to synthesize the phenazine carboxylic acid directly from 2,4′-diaminodiphenylamine-4-carboxylic acid (IId). 4′-Amino-2-nitrodiphenylamine-4-carboxylic acid (IIc) could be obtained by acid or alkaline hydrolysis of 4-acetamido-4′-cyano-2′-nitrodiphenylamine (IIe) which was prepared by the condensation of 4-bromo-3-nitrobenzonitrile with *p*-aminoacetanilide. Alternatively, 4-bromo-3-nitrobenzoic acid, in which the halogen atom is much less reactive than in the corresponding nitrile, could be condensed with *p*-phenylenediamine to give the required compound directly or with *p*-aminoacetanilide giving the acetamido compound (IIf) which was readily hydrolysed. 2,4′-Diaminodiphenylamine-4-carboxylic acid (IId), obtained by catalytic hydrogenation, was readily oxidized in acid solution by ferric chloride to a product which, by paper chromatography, was identical with that obtained by the hydrolysis of 2-amino-8-cyanophenazine (I, R = CN). All attempts to isolate the product, however, were abortive and it seemed likely that the aminophenazine carboxylic acid, if present, was complexed with ferric iron.

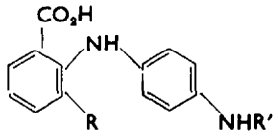
We therefore reverted to our original method utilizing nitrobenzene as both a solvent and an oxidizing agent on 2,4′-diaminodiphenylamine-4-carboxylic acid (IId). As with the corresponding nitrile, the oxidation was slow, but it could be accelerated by the addition of palladium charcoal as a hydrogen transfer catalyst. The product separated from the nitrobenzene on cooling as a gelatinous, amorphous solid which could not be crystallized. Paper chromatography showed it to be identical with the material obtained by the other synthesis. In spite of numerous attempts to purify it, no satisfactory analysis could be obtained. Even so, it was successfully converted to the methyl ester which was also obtained from methyl 4-bromo-3-nitrobenzoate, through methyl 2,4′-diaminodiphenylamine-4-carboxylate, by a route analogous to that used for the parent acid. Hydrolysis of the purified ester, however, produced an intractable acid again.

It seemed probable that the known 2-chloro-8-cyanophenazine[8] would provide a ready route to 8-aminophenazine-2-carboxylic acid by nucleophilic displacement of the halogen[9,10] and simultaneous hydrolysis of the cyano group upon heating in

[6] T. J. F. Mattaar, *Rec. Trav. Chim.* **41**, 24 (1922).
[7] G. Gaertner and F. G. Holliman, to be published.
[8] G. G. Coker, S. G. P. Plant and P. B. Turner, *J. Chem. Soc.* 110 (1951).
[9] I. J. Pachter and M. G. Kloetzel, *J. Amer. Chem. Soc.* **74**, 971 (1952).
[10] A. Gray and F. G. Holliman, *Tetrahedron* **18**, 1095 (1962).



III

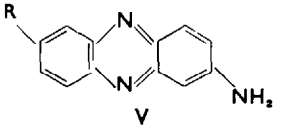


IV

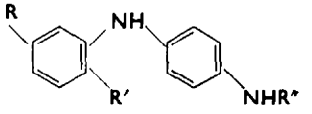
aqueous ammonia. Although indications were obtained that this was so, the route was abandoned as being insufficiently general.

The direct route to 7-aminophenazine-1-carboxylic acid (III) proved successful. 2-Bromo-3-nitrobenzoic acid condensed with *p*-phenylenediamine to give 4′-amino-6-nitrodiphenylamine-2-carboxylic acid (IV, R = NO_2, R′ = H). The yield was variable and low, however, possibly due to the reductive dehalogenating effect of *p*-phenylenediamine in Ullmann reactions,[11] and the alternative route, involving the condensation of the bromo acid with *p*-aminoacetanilide followed by hydrolysis of the resulting 4′-acetamido-6-nitrodiphenylamine-2-carboxylic acid (IV, R = NO_2, R′ = Ac) was more satisfactory. Oxidative cyclization of 4′,6-diaminodiphenylamino-2-carboxylic acid (IV, R = NH_2, R′ = H) gave 7-aminophenazine-1-carboxylic acid which, unlike its isomer, readily crystallized on cooling a nitrobenzene solution.

We now turned our attention to the synthesis of 7-aminophenazine-2-carboxylic acid (V, R = CO_2H). The direct route, through 4′,-6-diaminodiphenylamine-3-carboxylic acid (VIa), was unsuccessful as we failed to condense 3-bromo-4-nitrobenzoic acid with either *p*-phenylenediamine or *p*-aminoacetanilide, although a wide variety of conditions were tried. We therefore attempted the synthesis of the corresponding nitrile, 2-amino-7-cyanophenazine (V, R = CN).



V



VIa, R = CO_2H, R′ = NH_2, R″ = H.
VIb, R = CN, R′ = NO_2, R″ = Ac.
VIc, R = CN, R′ = NH_2, R″ = H.

The halogen atom in 3-bromo-4-nitrobenzonitrile proved insufficiently reactive to condense with *p*-phenylenediamine under relatively mild conditions, while harsher conditions failed to yield the desired product, again probably on account of reductive dehalogenation.[11] With *p*-aminoacetanilide, vigorous conditions could be used and successfully gave 4-acetamido-3′-cyano-6′-nitrodiphenylamine (VIb) which was hydrolysed to the required 4-amino compound. The 2,4′-diamino-5-cyanodiphenylamine (VIc), obtained by catalytic hydrogenation, appeared to be less susceptible to atmospheric oxidation than the 4-cyano isomer (IIb). Like the latter, however, it was readily oxidized in hot, acid solution by ferric chloride, 2-amino-7-cyanophenazine hydrochloride being precipitated. Alkaline hydrolysis of the cyanophenazine gave 7-aminophenazine-2-carboxylic acid; again, as with the 8-amino isomer, all attempts to crystallize it failed, but the acid was obtained analytically pure as was its methyl ester.

[11] A. A. Goldberg and W. Kelly, *J. Chem. Soc.* 102 (1046).

EXPERIMENTAL

M.ps. are uncorrected

4-Chloro (and bromo) -3-nitrobenzonitrile

It is unnecessary to use freshly distilled nitric acid as specified by Dunlop *et al.*[12] 4-Chlorobenzonitrile (20 g) in fuming HNO_3 (100 cc) was treated with conc H_2SO_4 (100 cc) keeping the temp below 20°. After 30 min at room temp, the mixture was poured into water. An almost quantitative yield of practically pure 4-chloro-3-nitrobenzonitrile was obtained.

The bromo compound was prepared in a similar way using 100 cc of each acid to 16 g of the nitrile.

4-Cyano-2,4'-dinitrodiphenylamine

4-Bromo-3-nitrobenzonitrile (2·3 g), *p*-nitroaniline (1·4 g) and anhydrous sodium acetate (3 g) in intimate mixture were heated at 200° for 30 min. The cooled product was extracted with hot ethanol (200 cc). The extract, on cooling, deposited golden-brown prisms of the *diphenylamine* (0·7 g, 29%) which was recrystallized (acetic acid) to m.p. 206–208° (Found: C, 55·2; H, 2·9; N, 19·8. $C_{13}H_8N_4O_4$ requires: C, 54·9; H, 2·8; N, 19·7%).

4-Amino-4'-cyano-2'-nitrodiphenylamine

(A) The method of Mattaar[6] was modified to avoid contamination of the product by *p*-phenylenediamine hydrobromide, which occurred when 4-bromo-3-nitrobenzonitrile was used in place of the corresponding chloro compound. 4-Bromo-3-nitrobenzonitrile (4 g) was added to a solution of *p*-phenylenediamine (2·2 g) in ethanol (150 cc) containing anhydrous potassium carbonate (2 g). After being refluxed for 2 hr, the hot mixture was filtered, the filtrate on cooling giving 4-amino-4'-cyano-2'-nitrodiphenylamine (3·4 g, 76%) as orange plates and as dark red needles. Both crystalline forms were again obtained on recrystallization (ethanol), and both had the same m.p. 158·5–159·5° (Mattaar[6] m.p. 158°).

(B) 4-Acetamido-4'-cyano-2'-nitrodiphenylamine (1 g) was suspended in 5 N HCl (20 cc). A little alcohol was added in order to wet the solid and the suspension was then refluxed for 3·5 hr. The mixture, containing the orange hydrochloride, was diluted with water (200 cc), made alkaline with 2 N NaOH and gently warmed. The precipitated free base was recrystallized (EtOH aq) and was again obtained as both orange plates and dark red needles, m.p. 158·5–159·5° (Found: C, 61·8; H, 4·1; N, 22·1. $C_{13}H_{10}H_4O_2$ requires: C, 61·4; H, 3·9; N, 22·0%).

4-Acetamido-4'-cyano-2'-nitrodiphenylamine

An intimate mixture of 4-chloro-3-nitrobenzonitrile (24 g), *p*-aminoacetanilide (20 g) and anhydrous sodium acetate (10·8 g) was heated at 100° for 1 hr, the colour rapidly becoming deep brick red. The cooled mixture was broken up, extracted with water, and the dark red, insoluble material was recrystallized (ethanol) to give *4-acetamido-4'-cyano-2'-nitrodiphenylamine* (24·5 g, 65%) as both orange prisms and long, dark red needles. Both crystalline forms, separated by hand picking, had m.p. 212·5–215 and similar analyses (Found: (orange form) C, 60·3; H, 4·0; N, 19·1; (red form) C, 61·4; H, 4·8; N, 18·7. $C_{15}H_{12}N_4O_3$ requires: C, 60·8; H, 4·05; N, 18·9%).

It was identical (m.p. and mixed m.p.) with the compound prepared by acetylation (acetic anhydride) of the corresponding aminonitrodiphenylamine.

4-Acetamido-2'-amino-4'-cyanodiphenylamine

The corresponding nitrodiphenylamine was catalytically hydrogenated (ethanol, PtO_2) the product separating during the reaction. The collected material, together with a further quantity obtained by evaporation of the solvent from the filtrate, was recrystallized (AcOH aq) to give 4-acetamido-2'-amino-4'-cyanodiphenylamine as pale pink needles m.p. 242–244° (Found: C, 67·3; H, 5·2; N, 21·35. $C_{15}H_{14}N_4O$ requires: C, 67·7; H, 5·3; N, 21·0%).

2,4'-Diamino-4-cyanodiphenylamine

(A) 4-Amino-4'-cyano-2'-nitrodiphenylamine (5 g) in ethanol (100 cc) was hydrogenated over Pd–charcoal. The *diaminodiphenylamine* (2·2 g) separated from the solution and a further quantity (1·7 g)

[12] H. G. Dunlop, T. F. Macrae and S. Horwood Tucker, *J. Chem. Soc.* 1672 (1934).

was obtained by evaporation of the filtrate. Recrystallization (EtOH aq, charcoal) gave silvery plates, m.p. 161–164° (Found: C, 68·9; H, 5·4; N, 25·55. $C_{13}H_{13}N_4$ requires: C, 69·6; H, 5·4; N, 25·0%).

Acetylation (acetic anhydride) gave the *diacetyl derivative*, obtained as colourless needles from dil. acetic acid (charcoal), m.p. 248–250° with resolidification and final m.p. 301–304° (Found: C, 65·8; H, 5·3. $C_{17}H_{16}N_4O_2$ requires: C, 66·2; H, 5·2%).

(B) 4-Cyano-2,4′-dinitrodiphenylamine was hydrogenated (ethanol, Pd–charcoal). Evaporation of the filtrate gave a brown solid, m.p. 157–161°, unchanged by admixture with a sample of the diaminodiphenylamine prepared as in (A) above. The diacetyl derivative had m.p. 246–248° with resolidification and final m.p. 300–305 (Found: C, 66·6; H, 5·3; N, 18·0. $C_{17}H_{16}N_4O_2$ requires: C, 66·2; H, 5·2; N, 18·2%).

An attempt to prepare this compound by the hydrolysis of 4′-acetamido-2′-amino-4′-cyanodiphenylamine was unsuccessful.

2-Amino-8-cyanophenazine

(A) A solution of 2,4′-diamino-4-cyanodiphenylamine (1 g) in 0·1 N HCl was heated on a steam bath. Ferric chloride (6 cc, 60% aqueous solution) was added dropwise with shaking, the solution becoming a deep permanganate colour and a dark solid being precipitated. Heating was continued for 15 min after completion of the addition of the oxidizing agent and the mixture was then chilled in ice. The very dark hydrochloride was filtered off (1·13 g, 99%). The free base (0·9 g, 92%), liberated by treatment of an aqueous suspension of the hydrochloride with aqueous ammonia, recrystallized (toluene, charcoal) as lustrous, red, feathery plates, m.p. 272–274° (Found: C, 70·6; H, 3·9; N, 24·8. $C_{13}H_8N_4$ requires: C, 70·9; H, 3·6; N, 25·45%).

(B) A solution of 2,4′-diamino-4-cyanodiphenylamine (1·3 g) in nitrobenzene (100 cc) containing Pd–charcoal (5%, 0·5 g) was refluxed for 20 hr. The catalyst was filtered off and the nitrobenzene removed in steam. The crude phenazine (0·96 g) recrystallized (toluene) as red, feathery plates (0·38 g, 34%), m.p. 273–275°.

4′-Acetamido-2-nitrodiphenylamine-4-carboxylic acid

4-Bromo-3-nitrobenzoic acid[13] (3 g), *p*-aminoacetanilide (1·83 g) and anhydrous sodium acetate (1 g), in intimate mixture, were heated at 145° for 30 min. The cooled product was dissolved in aqueous ammonia, the solution filtered and the *diphenylamine carboxylic acid* reprecipitated from the filtrate with acetic acid. Recrystallization (dil. acetic acid) gave 2·8 g (75%) of dark red plates m.p. 265–266° (Found: C, 56·7; H, 4·4; N, 13·4. $C_{15}H_{13}N_3O_5$ requires: C, 57·1; H, 4·1; N, 13·3%).

4′-Amino-2-nitrodiphenylamine-4-carboxylic acid

(A) *From 4-acetamido-4′-cyano-2′-nitrodiphenylamine.* The acetamidocyanodiphenylamine (0·5 g) in ethanol (6 cc) was treated with KOH aq (75% w/v soln, 10 cc) which caused immediate dissolution. The solution was heated under reflux for 1 hr, after 10 min the original purple colour becoming red brown. The cooled solution was diluted and the ethanol removed by distillation. The residue was filtered and acidified with acetic acid. The resulting precipitate was recrystallized (ethanol) to give bright orange needles of *4′-amino-2-nitrodiphenylamine-4-carboxylic acid* m.p. 241–243°, analysis indicating that the compound was isolated as a hydrate (Found: C, 52·6; H, 4·1; N, 14·2. $C_{13}H_{11}N_3O_4$, H_2O requires: C, 53·6; H, 4·5; N, 14·4%) which was hydroscopic after drying (Found: C, 57·7; H, 4·0; N, 15·4. $C_{13}H_{11}N_3O_4$ requires: C, 57·2; H, 4·0; N, 15·4%).

Acid (conc HCl, 11 cc) hydrolysis, although much slower (13 hr), was also successful.

(B) *From 4′-acetamido-2-nitrodiphenylamine-4-carboxylic acid.* The acetamido compound (1 g) in 5 N HCl (50 cc) was heated under reflux for 8 hr. A clear solution was never obtained, orange needles being present at the end of the reflux period. After dilution with water (100 cc) the mixture was boiled, filtered and cooled to give a crystalline precipitate of the hydrochloride of the aminodiphenylamine carboxylic acid. This was filtered off, suspended in water, and the free base liberated with sodium acetate. Recrystallization gave 0·32 g (37%) m.p. 236–237° undepressed by admixture with a sample from (A) above.

Alkaline (2·5 N KOH, 20 cc) was much more rapid (15 min) but gave a lower yield (0·2 g).

[13] R. E. Buckles, R. Filler and L. Hilfman, *J. Org. Chem.* **17**, 233 (1952).

(C) A solution of 4-bromo-3-nitrobenzoic acid[18] (10 g) and *p*-phenylenediamine (8·7 g) in amyl alcohol (120 cc) was heated under reflux at 140–150° for 1 hr. The solvent was removed in steam and the orange brown solid remaining was filtered off after cooling. It was suspended in water (400 cc), and conc HCl (100 cc) added; the mixture was boiled with charcoal, filtered and cooled to give the hydrochloride of 4′-amino-2-nitrodiphenylamine-4-carboxylic acid which was collected and treated with a solution of sodium acetate to give the free base (8 g, 74%) which was recrystallized to give orange needles m.p. 236–238 undepressed by a mixture with a sample from (A) above (Found: N, 14·2%).

Methyl-4′-amino-2-nitrodiphenylamine-4-carboxylate

Methyl 4-bromo-3-nitrobenzoate[18] (2·6 g) and *p*-phenylenediamino (1·2 g) in ethanol (50 cc) were heated under reflux for 2 hr. Ethanol (150 cc) was added and the mixture heated to boiling, filtered and cooled to give the *diphenylamine ester* (1·5 g, 52%) as silky, dark red needles m.p. 175–179°, recrystallization (ethanol) raising the m.p. to 179–180° (Found: C, 58·8; H, 4·5; N, 14·4. $C_{14}H_{13}N_3O_4$ requires: C, 58·5; H, 4·5; N, 14·6%).

2,4′-*Diaminodiphenylamine-4-carboxylic acid*

4′-Amino-2-nitrodiphenylamine-4-carboxylic acid was hydrogenated (ethanol, Pd–C) and the major part of the diaminodiphenylamine carboxylic acid resulting crystallized out during the reaction. The solid was filtered off and, combined with the small amount obtained by removing the ethanol from the filtrate under red. press., was recrystallized (EtOH aq) to give *2,4′-diaminodiphenylamine-4-carboxylic acid* as grey needles m.p. 173·5–174° (Found: C, 64·4; H, 6·0; N, 17·4. $C_{13}H_{13}N_3O_2$ requires: C, 64·2; H, 5·35; N, 17·3%).

Acetylation (acetic anhydride–pyridine) gave the *diacetyl derivative* which was recrystallized (dil. acetic acid) as colourless needles m.p. 283–285° (Found: C, 62·2; H, 5·4. $C_{17}H_{17}N_3O_4$ requires: C, 62·4; H, 5·2%).

Methyl-2,4′-diaminodiphenylamine-4-carboxylate

Methyl 4′-amino-2-nitrodiphenylamine-4-carboxylate was hydrogenated (ethanol, Pd–C). The catalyst was removed by filtration and the solvent was removed from the filtrate under red. press. The residue was recrystallized (ethanol, charcoal) giving the *diaminodiphenylamine ester* as white needles m.p. 163·5–166° (Found: C, 65·0; H, 5·9; N, 16·35. $C_{14}H_{15}N_3O_2$ requires: C, 65·4; H, 5·8; N, 16·3%).

Acetylation by gentle warming with acetic anhydride gave the diacetyl derivative which recrystallized as colourless needles m.p. 221–222° (Found: C, 63·3; H, 5·5; N, 12·4. $C_{18}H_{19}N_3O_4$ requires: C, 63·3; H, 5·6; N, 12·3%).

Methyl 2-aminophenazine-8-carboxylate

(A) A solution of 2,4′-diaminodiphenylamine-4-carboxylic acid (1 g) in nitrobenzene (100 cc) was boiled under reflux in the presence of Pd–charcoal (5%, 0·5 g) for 15·5 hr. The catalyst was filtered off and the cooled filtrate deposited a gelatinous precipitate (0·6 g) which was filtered off and washed with ether. It was practically insoluble in all the usual solvents; although soluble in hot nitrobenzene, the cooled solution again deposited a non-crystalline solid, and material repeatedly treated in this way failed to give a satisfactory analysis for 2-aminophenazine-8-carboxylic acid and did not melt below 360°. That the latter compound was present was shown by esterification by heating the solid (0·1 g) with dry methanol (50 cc) in the presence of conc H_2SO_4 (1 cc) for 2 hr. Most of the methanol was removed by distillation, the residue was diluted with water and the purple solution made alkaline with ammonia to precipitate the crude *ester*. Recrystallization (toluene) gave long, lustrous, red needles m.p. 256–257° (Found: C, 66·1; H, 4·6; N, 15·8. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·35; N, 16·6%).

(B) (With D.J.H.B.) 2-Amino-8-cyanophenazine (0·2 g) and sodium hydroxide (4 g) in a mixture of water (5 cc) and ethanol (15 cc) were refluxed for 1 hr. The mixture was diluted to 50 cc with water and filtered hot. The pH was brought to 5 and the resulting precipitate collected and dried. It was dissolved in hot nitrobenzene, the cooled solution then depositing a gelatinous solid which was filtered off and washed with ether. It failed to give a satisfactory analysis and did not melt below 360°. It was esterified by a method similar to that described under (A). The recrystallized product had m.p.

256° undepressed by admixture with the sample prepared in (A) above. The I.R. spectra (KCl disc) of the two samples of ester were identical.

(C) Methyl 4′-amino-2-nitrodiphenylamine-4-carboxylate (1·3 g) was hydrogenated (ethanol, Pd–C). The catalyst was removed, nitrobenzene (100 cc) was added to the filtrate, the ethanol was removed by distillation. To the residue, Pd–charcoal (5%, 0·5 g) was added and the mixture boiled under reflux for 18 hr. After removal of the catalyst, the nitrobenzene was removed under red. press. and the residual solid was recrystallized (toluene) to give 0·34 g (29%) of the ester m.p. 252–254°. Identity with the sample obtained as in (A) was shown by mixed m.p. and I.R. spectra (KCl disc).

4′-Acetamino-6-nitrodiphenylamine-2-carboxylic acid

An intimate mixture of 2-bromo-3-nitrobenzoic acid[14] (25 g), *p*-aminoacetanilide (15·3 g) and anhydrous sodium acetate (8·4 g) was heated at 135–145° for 30 min. The cooled, powdered mixture was extracted with ethanol. The extract was diluted with water and chilled to give 25 g (80%) of *4′-acetamido-6-nitrodiphenylamine-2-carboxylic acid* which recrystallized (dil. ethanol) as short, thick, orange-red needles m.p. 217·5–218° (Found: C, 56·7; H, 4·1; N, 13·3. $C_{15}H_{13}N_3O_5$ requires: C, 57·1; H, 4·1; N, 13·3%).

4′-Amino-6-nitrodiphenylamine-2-carboxylic acid

(A) 2-Bromo-3-nitrobenzoic acid[14] (2 g) and *p*-phenylenediamine (1·75 g) in amyl alcohol (25 cc) were refluxed for 1 hr, the amyl alcohol then being removed in steam. The cooled residue was filtered and the crude, green-brown solid had m.p. 231–231·5. Recrystallization (dil. acetic acid) entailed much loss and gave *4′-amino-6-nitrodiphenylamine-2-carboxylic acid* m.p. 233–234·5° (Found: C, 57·2; H, 4·1; N, 15·3. $C_{13}H_{11}N_3O_4$ requires: C, 57·2; H, 4·0; N, 15·4%). A better method of purification entailed the addition of potassium carbonate to the residue from the steam distillation, filtration from insoluble matter and reprecipitation of the orange-yellow diphenylamine carboxylic acid from the filtrate by acidification with acetic acid. The amino acid was next dissolved in hot 2 N HCl; the solution was boiled with charcoal and filtered, and the filtrate, on cooling, deposited yellow needles of the hydrochloride from which the free amino acid was obtained by treatment with sodium acetate. Using this method of purification, the yield was 49% of golden-yellow, elongated plates m.p. 234–235°.

(B) A solution of 4′-acetamido-6-nitrodiphenylamine-2-carboxylic acid (4 g) in 2 N NaOH aq (80 cc) was boiled under reflux for 1 hr and then cooled and acidified with acetic acid. The crude, yellow-brown 4′-amino-6-nitrodiphenylamine-2-carboxylic acid (2·8 g, 81%) was recrystallized (dil. acetic acid) with much loss giving golden elongated plates m.p. 234–234·5° (Found: C, 57·2; H, 4·1; N, 15·3%).

4′,6-Diaminodiphenylamine-2-carboxylic acid

Hydrogenation of 4′-amino-6-nitrodiphenylamine-2-carboxylic acid (2·5 g) in ethanol (100 cc) with Pd–charcoal led to the precipitation of the diaminodiphenylamine carboxylic acid (2 g). This was easily oxidized in the air but could be recrystallized from dil. ethanol or from ethyl cellosolve (preferably in an atm. of N_2) giving needles, slightly coloured brown due to aerial oxidation, m.p. 245–246° (Found: C, 63·6; H, 5·3; N, 17·1. $C_{13}H_{13}N_3O_2$ requires: C, 64·2; H, 5·35; N, 17·3%).

7-Aminophenazine-1-carboxylic acid

4′,6-Diaminodiphenylamine-2-carboxylic acid (2 g) in nitrobenzene (400 cc) and Pd–charcoal (5%, 2 g) was heated under reflux for 4 hr. The hot solution was filtered from the catalyst and, on cooling, deposited red needles of *7-aminophenazine-1-carboxylic acid* (1·1 g, 54%) m.p. 340° d which were recrystallized from nitrobenzene (Found: C, 65·5; H, 3·8; N, 17·4. $C_{13}H_9N_3O_2$ requires: C, 65·3; H, 3·8; N, 17·6%).

Methyl-7-aminophenazine-1-carboxylate

A solution of 7-aminophenazine-1-carboxylic acid (0·5 g) in methanol (100 cc) and conc H_2SO_4 (1 cc) was boiled under reflux for 2 hr. Most of the methanol was then removed by distillation and the cooled residue was diluted with water. The small amount of insoluble material was filtered off and the filtrate made alkaline with NH_4OH aq. The precipitated ester was recrystallized (toluene) to give

[14] P. J. Culhane, *Organic Syntheses* Coll. Vol. I, 125.

red needles m.p. 202–204° (Found: C, 66·7; H, 4·4; N, 16·4. $C_{14}H_{11}N_3O_2$ requires: C, 16·4; H, 4·35; N, 16·6%).

4-Acetamido-3′-cyano-6′-nitrodiphenylamine

A mixture of 3-bromo-4-nitrobenzonitrile[15] (10·2 g), *p*-aminoacetanilide (7 g) and potassium acetate (3·5 g) was heated at 120–130° for 5 hr. The dark product was cooled, ground and extracted with aqueous acetic acid. The diphenylamine carboxylic acid crystallized from the cooled extract and was recrystallized (dil. acetic acid) as red brown needles m.p. 208–209° (Found: C, 60·6; H, 4·1; N, 18·7. $C_{15}H_{12}N_4O_2$ requires: C, 60·8; H, 4·1; N, 18·9%).

4-Amino-3′-cyano-6′-nitrodiphenylamine

4-Acetamido-3′-cyano-6′-nitrodiphenylamine (3 g) in 5 N HCl (60 cc) was treated with ethanol (10 cc) to make the solid wettable. The mixture was refluxed for 4 hr, the solid becoming red-orange in colour, but not dissolving. The mixture was cooled and the solid hydrochloride collected and dissolved in hot water. *4-Amino-3′-cyano-6′-nitrodiphenylamine* (2·1 g, 84%) was liberated with sodium hydroxide and recrystallized (EtOH aq, charcoal) to give dark red, lustrous needles m.p. 145–147° (Found: C, 61·2; H, 4·05; N, 21·9. $C_{13}H_{10}N_4O_2$ requires: C, 61·4; H, 3·9; N, 22·05%).

2,4′-Diamino-5-cyanodiphenylamine

Hydrogenation (ethanol, Pd–C) of 4-amino-3′-cyano-6′-nitrodiphenylamine gave the diaminodiphenylamine which remained as a blue-black glass after removal of the solvent. Recrystallization (EtOH aq) gave the *diaminodiphenylamine* (76%) as almost colourless needles m.p. 156–158° (Found: C, 69·5; H, 5·3; N, 25·2. $C_{13}H_{12}N_4$ requires: C, 69·6; H, 5·4; N, 25·0%).

2-Amino-7-cyanophenazine

A solution of 2,4′-diamino-5-cyanodiphenylamine (1 g) in 0·33 N HCl (30 cc) was heated on a steam bath. 1·01 M $FeCl_3$ aq (16 cc) was slowly added to the hot solution with swirling. An intense permanganate colour was produced immediately and a heavy, dark precipitate was formed. The mixture was heated for a further 15 min, chilled in ice and then filtered. The dark solid, presumably the hydrochloride of the aminophenazine, was suspended in water and treated with Na_2CO_3 aq to produce the free base. Recrystallization (toluene) gave red needles of *2-amino-7-cyanophenazine* (0·3 g, 30%) m.p. 289–291 (when placed in the bath at 230°) (Found: C, 71·0; H, 3·7; N, 24·8. $C_{13}H_8N_4$ requires: C, 70·9; H, 3·6; N, 25·45%).

7-Aminophenazine-2-carboxylic acid (with D. J. H. B.)

The nitrile (0·25 g) in ethanol (18 cc) together with a solution of sodium hydroxide (5 g) in water (6·5 cc) were refluxed for 1 hr. The mixture was diluted with water, heated to boiling and filtered. The cooled filtrate was brought to pH 4, *7-aminophenazine-2-carboxylic acid* being precipitated as a dark red powder (0·22 g, 80%). It was insoluble in water and most organic solvents; it dissolved in hot nitrobenzene and was reprecipitated on cooling as an amorphous solid, all attempts to produce a crystalline material meeting with failure. The material obtained by cooling a hot nitrobenzene solution appeared to be a single substance by paper chromatography [butanol–conc HCl (4 : 1) saturated with water and butanol-acetic acid-water (5 : 1 : 4)] (Found: C, 65·1; H, 4·05; N, 17·5. $C_{13}H_9N_3O_2$ requires: C, 65·3; H, 3·75; N, 17·6%).

Methyl 7-aminophenazine-2-carboxylate (with D. J. H. B.)

Conc H_2SO_4 (1 cc) was added to a solution of 7-aminophenazine-2-carboxylic acid (98 mg) in dry methanol (50 cc) and the mixture was boiled under reflux for 2 hr. Most of the methanol was removed by distillation, the residue was cooled, diluted to 50 cc with water and the solution made alkaline with ammonia. The precipitated *ester* was recrystallized (toluene) to red needles m.p. 264–265° (Found: C, 66·6; H, 4·65; N, 16·4. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·35; N, 16·6%).

Acknowledgements—Financial assistance from the Staff Research Fund of the University of Cape Town for the purchase of chemicals and equipment and from the South African Council for Scientific and Industrial Research for the employment of a research assistant (B. A. J.) are gratefully acknowledged.

[15] J. D. Bowers, F. F. Stephens and D. G. Wibberley, *J. Chem. Soc.* 3341 (1950).