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PHENAZINES—IV

THE SYNTHESIS OF 3-AMINOPHENAZINE-1-, 3-AMINOPHENAZINE-2- AND 8-AMINOPHENAZINE-1-CARBOXYLIC ACIDS*

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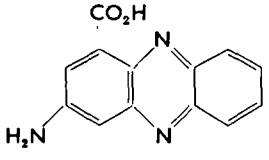
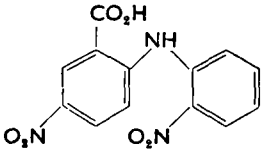
Abstract—The oxidative cyclization in boiling nitrobenzene of 4,6-diaminodiphenylamine-2-carboxylic acid gave 3-aminophenazine-1-carboxylic acid. 4,6-Diaminodiphenylamine-3-carboxylic acid underwent decarboxylation, but the methyl ester gave methyl 3-aminophenazine-2-carboxylate from which the acid was obtained. 2,4-Diaminodiphenylamine-3′-carboxylic acid gave a mixture of 7-aminophenazine-2- and 8-aminophenazine-1-carboxylic acids from which the pure acids were separated and oriented. 8-Aminophenazine-1-carboxylic acid, together with some 1,8-diaminoacridone, was also obtained from 3′,6-diaminodiphenylamine-2-carboxylic acid.

THE syntheses of 7-aminophenazine-1-, 7-aminophenazine-2- and 8-aminophenazine-2-carboxylic acids have already been described.[1] The first and last of these were effected by a new method of phenazine synthesis involving the cyclization of 2,4′-diaminodiphenylamines in boiling nitrobenzene.[2,3] Attempts to extend this approach to other members of the series, however, were frustrated by difficulties in the synthesis of the required 2,4′-dinitrodiphenylamine carboxylic acids. For example, the synthesis of 3-aminophenazine-1-carboxylic acid (I) would require 2′,4-dinitrodiphenylamine-2-carboxylic acid (II). Although Goldstein and Rodel[4] describe the preparation of this compound, we failed to prepare it satisfactorily, obtaining low yields of product difficult to purify. Various modifications of the method, such as using the 2-fluoro- in place of the 2-bromo-5-nitrobenzoic acid in the condensation with *o*-nitroaniline, also failed, as did attempts to condense the halo-acids with *o*-phenylenediamine or *o*-aminoacetanilide or to condense 2-bromo-5-nitrobenzonitrile with *o*-phenylenediamine or *o*-nitroaniline.



I



II

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

† This paper is abstracted from the dissertation submitted by D. J. H. Brock for the degree of Ph.D., University of Cape Town, September 1962.

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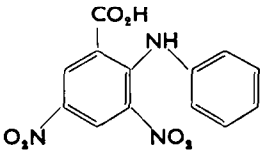
[1] Part III. F. G. Holliman, B. A. Jeffery and D. J. H. Brock, *Tetrahedron* **19**, 1841 (1963).

[2] A. Gray, G. Gaertner and F. G. Holliman, *Tetrahedron Letters* No. 7, 24 (1959).

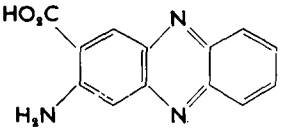
[3] G. Gaertner, A. Gray and F. G. Holliman, *Tetrahedron* **18**, 1105 (1962).

[4] H. Goldstein and W. Rodel, *Helv. Chim. Acta* **9**, 765 (1926).

Our fundamental investigations on the cyclization of 2-aminodiphenylamines subsequently showed, however, that the more easily prepared 2,4-diaminodiphenylamines would also produce 2-aminophenazines[3] and successful routes to the other 2-aminophenazine carboxylic acids were thereby opened up. Thus, 4,6-dinitrodiphenylamine-2-carboxylic acid[5] (III) was catalytically hydrogenated to the diamino compound which, refluxed for 7 hours in nitrobenzene, gave a 50% yield of crystalline 3-aminophenazine-1-carboxylic acid (I).



III



IV

3-Aminophenazine-2-carboxylic acid (IV) was obtained by a similar route, except that a minor modification had to be introduced to avoid decarboxylation occurring during the cyclization step: when 4,6-dinitrodiphenylamine-3-carboxylic acid[6a] was reduced to the diamino compound and then refluxed in nitrobenzene, the only product isolated was 2-aminophenazine itself. Accordingly, the methyl ester of 3-bromo-4,6-dinitrobenzoic acid, which was prepared from *m*-bromobenzoic acid under conditions similar to those used by Goldstein and Stamm for the nitration of *m*-chlorobenzoic acid,[6b] was condensed with aniline to give methyl 4,6-dinitrodiphenylamine-3-carboxylate. The latter, by the usual method, gave the methyl ester of 3-aminophenazine-2-carboxylic acid from which the acid itself was readily obtained by alkaline hydrolysis. Like 7- and 8-aminophenazine-2-carboxylic acids, this isomer was obtained in an amorphous state and resisted all attempts at crystallization.

The reduction and cyclization of 2',4'-dinitrodiphenylamine-3-carboxylic acid[7,8] (V) can theoretically give two isomers, 7-aminophenazine-2-carboxylic acid (VI) and 8-aminophenazine-1-carboxylic acid (VII), whereas that of 2,4'-dinitrodiphenylamine-3-carboxylic acid (VIII) should give 8-aminophenazine-1-carboxylic acid (VII) unambiguously. Attempts to follow this latter route, however, were unattractive as two methods for preparing the intermediate 3-bromo-2-nitrobenzoic acid require tedious isomer separations[9,10] whilst a third method failed in the deamination of 3-bromo-6-nitroanthranilic acid.[11] The expected mixture of isomers was indeed obtained from 2',4'-dinitrodiphenylamine-3-carboxylic acid (V), the two aminophenazine carboxylic acids expected, (VI and VII), being produced in approximately equal proportions. Although closely similar to each other and inseparable by physical means, the two isomers were separated by treatment of the crude mixture with methanol

[5] F. Ullmann, *Liebigs Ann.* **366,** 83 (1909).

[6] [a] H. Goldstein and R. Stamm, *Helv. Chim. Acta* **35,** 1470 (1952); [b] cf. Idem. *Ibid.* **35,** 1330 (1952).

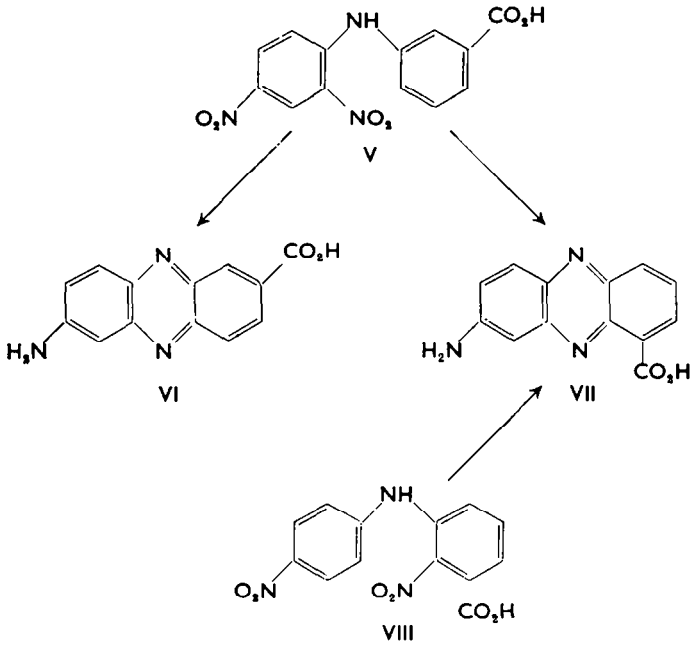
[7] B. Linke, *J. Prakt. Chem.* **91,** 202 (1915).

[8] H. Brauniger and K. Spangenberg, *Pharmazie* **12,** 335 (1957).

[9] H. Hübner, J. Ohly and O. Philipp, *Liebigs Ann.* **143,** 234 (1867); P. Friedländer, S. Bruckner and G. Deutsch, *Ibid.* **388,** 23 (1912).

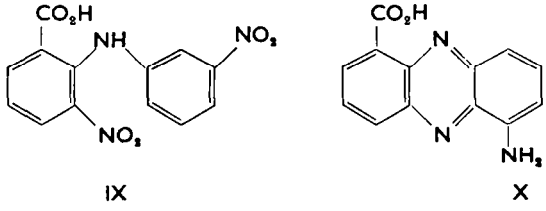
[10] H. Burton. F. Hammond and J. Kenner, *J. Chem. Soc.* 1802 (1926); S. Coffey. *Ibid.* 637 (1926).

[11] J. L. E. Erickson, J. M. Dechary and T. R. Pullig, *J. Amer. Chem. Soc.* **74,** 5621 (1952).



in the presence of sulphuric acid: one of the acids was quantitatively converted to its methyl ester while the other remained unchanged. The methyl ester proved to be identical with that from 7-aminophenazine-2-carboxylic acid.[1]

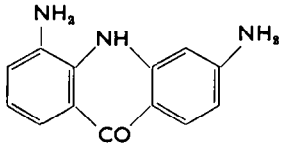
If therefore seemed almost certain that the unreacted acid (which, however, could be esterified by diazomethane in dimethylformamide) was VII, but to establish this point beyond doubt, an independent synthesis from another diphenylamine was sought. It had been shown[12] that 2,4- and 2,4′-diaminodiphenylamines are not the only possible intermediates for the synthesis of 2-aminophenazine; 2,3′-diaminodiphenylamine also gives 2-aminophenazine although, as expected, it is accompanied by 1-aminophenazine. Accordingly, 3′,6-dinitrodiphenylamine-2-carboxylic acid[13] (IX) was synthesized. As use of 2-bromo-3-nitrobenzoic acid, in place of the chloro



compound used by Goldberg and Kelly,[13] in the Ullmann condensation with *o*-nitroaniline gave a product which could not be sufficiently purified for a completely successful hydrogenation, we used the ester of the diphenylamine carboxylic acid for the reduction and cyclization steps. The 8-aminophenazine-1-carboxylic acid methyl ester so obtained proved to be identical with that from the second of the two isomeric

[12] G. Gaertner and F. G. Holliman, to be published.
[13] A. A. Goldberg and W. Kelly, *J. Chem. Soc.* 595 (1947).

aminophenazine carboxylic acids described above and thus established its orientation. Also present in the reaction product was the expected methyl 6-aminophenazine-1-carboxylate (X), the structure of which was confirmed by hydrolysis to the acid and decarboxylation to 1-aminophenazine. The ratio of *para* to *ortho* (relative to the 3′-amino group) ring-closure, leading to the 2-amino and 1-aminophenazine derivatives respectively, was 10:1, in marked contrast to the 1:3 ratio observed when the carbomethoxyl group is absent.[12]



XI

3′,6-Diaminodiphenylamine-2-carboxylic acid itself, obtained by the partial reduction of the crude dinitrodiphenylamine, by heating in nitrobenzene solution, led to a mixture of 8-aminophenazine-1-carboxylic acid (VII) and 1,8-diaminoacridone (XI), the identity of the latter being established by independent synthesis.[13] The cyclization of diphenylamine-2-carboxylic acids to acridones, normally an acid catalysed reaction passing through a carbonium ion intermediate,[14] appears unprecedented under these conditions.

EXPERIMENTAL

M.ps. are uncorrected. Pet. ether refers to the fraction boiling 100–120°. Chromatographic alumina was Peter Spence grade 0. Chromatographic solvents were: A, butanol–conc HCl (4 : 1, saturated with water); B, butanol–acetic acid–water (4 : 1 : 5); C, butanol–formic acid–water (95 : 5 saturated with water); D, butanol saturated with 1·5N ammonia.

Reduction of nitrodiphenylamines and the cyclization of aminodiphenylamines

In each case, the nitrodiphenylamine in absolute ethanol was hydrogenated at 30–40 lb/in² with PtO_2 or 5% Pd–charcoal as catalyst until a colourless solution was obtained. The solution was filtered into nitrobenzene, the ethanol and a small amount of nitrobenzene distilled off and the residual solution then heated under reflux with or without the addition of Pd–charcoal as catalyst.

3-*Aminophenazine*-1-*carboxylic acid*

4,6-Dinitrodiphenylamine-2-carboxylic acid[5] (1 g) was hydrogenated over Pd–charcoal and the product refluxed in nitrobenzene (125 cc) for 7 hr. After removal of the nitrobenzene in steam, the residue was made alkaline with ammonia and filtered. 3-*Aminophenazine*-1-*carboxylic acid* (0·40 g, 50%) was precipitated on bringing the filtrate to pH 6. Recrystallization (methanol) gave bright red needles, m.p. 304° (Found: C, 65·0; H, 3·9; N, 17·2. $C_{13}H_9N_3O_2$ requires: C, 65·3; H, 3·8; N, 17·6%).

Methyl 3-*aminophenazine*-1-*carboxylate* was prepared by refluxing the acid (0·151 g) in absolute methanol (75 cc) with a few drops conc H_2SO_4 for 2 hr. Excess methanol was distilled off, the residue treated with NH_4OH aq and the solid *ester* collected. It separated from toluene as red orange needles m.p. 230–235° (Found: C, 66·5; H, 4·9; N, 16·3. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·3; N, 16·6%).

3-*Bromo*-4,6-*dinitrobenzoic acid*

m-Bromobenzoic acid (10 g) in conc H_2SO_4 (100 cc) was warmed slowly to 50° with rapid stirring. Finely powdered potassium nitrate (5 g) was added in portions at such a rate that the temp. was kept between 50 and 65°. The solution was then heated cautiously to 105°, traces of potassium nitrate

[14] R. M. Acheson, *Acridines* p. 121. Interscience, New York (1956).

being added if any sign of darkening occurred. A further 20 g of potassium nitrate were then added, the temp. being kept between 105 and 110°; thereafter, the solution was heated to 125° for 30 min, cooled and poured onto ice (500 g). A portion of the crude acid was recrystallized twice (EtOH aq) to give pale yellow needles m.p. 190° (Goldstein and Stamm[6a] report m.p. 191° for this compound prepared from the corresponding chloroacid).

The methyl ester (m.p. 106°) was prepared as described by Goldstein and Stamm who quote m.p. 107°.[6a]

Methyl 4,6-*dinitrodiphenylamine*-3-*carboxylate*

Crude methyl 3-bromo-4,6-dinitrobenzoate (5 g) and freshly distilled aniline (25 cc) were heated at 100° for 1 hr. The solution was cooled and poured into 5N HCl (100 cc). Two recrystallizations of the precipitate from ethanol gave the *diphenylamine ester* (4 g, 77%) as yellow-orange plates, m.p. 142–146°. Further recrystallization raised the m.p. to 146–148°. (Found: C, 53·0; H, 3·3; N, 13·3. $C_{14}H_{11}N_3O_6$ requires: C, 53·0; H, 3·5; N, 13·2%).

Methyl 4,6-*diaminodiphenylamine*-3-*carboxylate*

Methyl 4,6-dinitrodiphenylamine-3-carboxylate (0·5 g) in absolute ethanol was hydrogenated at 3 atm. over PtO_2. The solvent was removed under red. press. and the residue recrystallized (pet. ether, charcoal) to give silver needles of the *diaminodiphenylamine ester*, m.p. 163–166°. (Found: C, 65·7; H, 5·9; N, 16·6. $C_{14}H_{15}N_3O_2$ requires: C, 65·4; H, 5·8; N, 16·3%).

Methyl 3-*aminophenazine*-2-*carboxylate*

Methyl 4,6-dinitrodiphenylamine-3-carboxylate (1·23 g) was reduced and the product refluxed in nitrobenzene (150 cc) in the presence of Pd–charcoal (1·2 g) for 32 hr. The volume of the solution was reduced *in vacuo* to about 10 cc and the oily solution adsorbed onto an alumnia column (2 × 30 cm). Development of the column with benzene removed the residual nitrobenzene. The main, red bond was eluted with ether, the solvent evaporated and the residue recrystallized (pet. ether) to give *methyl* 3-*aminophenazine*-2-*carboxylate* (0·32 g, 32%) as deep red clusters of needles, m.p. 235°. (Found: C, 66·6; H, 4·4; N, 16·9. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·3; N, 16·6%).

Reduction and cyclization of 4,6-dinitrodiphenylamine-3-carboxylic acid[6a] gave only 2-aminophenazine, identified by mixed m.p. and paper chromatography (solvent A).

3-*Aminophenazine*-2-*carboxylic acid*

The methyl ester (50 mg) in 3N NaOH (5 cc) was warmed at 100° for 30 min. The solution was diluted, filtered and cooled. The pH was adjusted to 5 to give a dark purple precipitate of 3-aminophenazine-2-carboxylic acid (quantitative recovery). Attempts to crystallize this product failed; it separated from a hot solution in nitrobenzene on cooling as an amorphous mass, which decomposed at 320°. (Found: C, 65·2; H, 4·0; N, 17·4. $C_{13}H_9N_3O_2$ requires: C, 65·3; H, 3·8; N, 17·6%).

Reduction of 2′,4′-*dinitrodiphenylamine*-3-*carboxylic acid, characterization of the diaminodiphenylamine and its cyclization*

The diphenylamine[7] in absolute ethanol was hydrogenated at 3 atm over 5% Pd–charcoal. The clear solution was filtered and the solvent removed under red. press. in a stream of N_2. Acetylation of the residue by reaction with acetic anhydride in the cold gave 2′,4′-*diacetamidodiphenylamine*-3-*carboxylic acid* for which no suitable solvent for recrystallization could be found. The washed, dried material had m.p. 194–196° (dec). (Found: C, 61·7; H, 5·3; N, 12·5. $C_{17}H_{17}N_3O_4$ requires: C, 62·4; H, 5·2; N, 12·8%).

A solution of the diaminodiphenylamine (from 3 g of the dinitrodiphenylamine) in nitrobenzene (375 cc) was refluxed for 10 hr. The solution was filtered and the nitrobenzene removed *in vacuo*. The residue was dissolved in a mininum of hot NH_4OH aq and the solution filtered and extracted with ether to remove residual nitrobenzene. The ammoniacal solution was brought to pH 5 and the precipitate collected by centrifugation.

The precipitate of mixed acids (1·75 g) was refluxed in dry methanol (400 cc) containing conc H_2SO_4 (4 cc) for 3 hr. The solution was concentrated by distillation, diluted and made alkaline with ammonia. The resulting precipitate was dissolved in nitrobenzene and passed through a column

(2 × 35 cm) of acid-washed, methanol-deactivated alumina: the nitrobenzene was removed with benzene and the phenazine eluted with ether. Repetition of the chromatography gave methyl 7-aminophenazine-2-carboxylate (0·300 g, 12%) which recrystallized (toluene) as red needles m.p. 264°. Paper chromatography of an aliquot of the crude ester followed by spectrophotometric estimation of the eluted spot indicated that the acid had been produced in a yield of 22% on the basis of quantitative esterification. The ester (0·170 g) in 3 N NaOH (8·5 cc) was refluxed for 2 hr. On cooling and acidifying the solution, 7-aminophenazine-2-carboxylic acid was obtained as a brick red precipitate (0·140 g, 87%); a hot nitrobenzene solution on cooling deposited the acid as an amorphous mass, m.p. above 360°. The IR spectra (KCl disc) of the acid and the ester were identical with those of the corresponding compounds prepared from the nitrile.[1]

Slow evaporation of the ammoniacal filtrate from the esterification released *8-aminophenazine-1-carboxylic acid* as dark red gleaming needles with a greenish sheen (0·450 g, 19%) m.p. 327° (dec). Two recrystallizations (nitrobenzene) raised the m.p. to 346° (dec) (Found: C, 65·3; H, 4·0; N, 17·5. $C_{13}H_8N_3O_2$ requires: C, 65·3; H, 3·8; N, 17·5%).

Methyl 8-aminophenazine-1-carboxylate was obtained by treating the acid (0·200 g) in dimethylformamide (50 cc) with an excess of ethereal diazomethane at 0°. The solvent was removed *in vacuo* and the residue recrystallized (benzene–pet. ether) to give the ester as deep red needles (0·170 g, 80%), m.p. 186–188° (Found: C, 66·7; H, 4·6; N, 16·6. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·3; N, 16·6%).

3′,6-Dinitrodiphenylamine-2-carboxylic acid

This compound was prepared by a method similar to that reported by Goldberg and Kelly[13] but with 2-bromo-3-nitrobenzoic acid[15] replacing the corresponding chloro acid. Repeated recrystallization (EtOH aq and AcOH aq) failed to raise the m.p. above 193° (Goldberg and Kelly[13] quote 196–198°) and chromatography on alumina was no more effective. This crude material could not be hydrogenated completely.

Methyl 3′,6-dinitrodiphenylamine-2-carboxylate

(A) Impure 3′,6-dinitrodiphenylamine-2-carboxylic acid (2·45 g) in ether (120 cc) was treated with excess ethereal diazomethane at 0°. The *methyl ester* crystallized slowly from the solution and after several hr the bright yellow needles (1·8 g, 70%) were collected; recrystallization (EtOH aq or AcOH aq) did not change the m.p. of 143–146° (Found: C, 52·5; H, 3·6; N, 13·2. $C_{14}H_{11}N_3O_6$ requires: C, 53·0; H, 3·5; N, 13·2%. A further crop of less pure material could be obtained from the filtrate

Esterification could not be effected with methanol as the solvent.

(B) Methyl 2-bromo-3-nitrobenzoate[16] (1·55 g), *m*-nitroaniline (1·25 g), anhydrous potassium carbonate (1·25 g) and copper powder (0·030g) were well mixed and heated at 190° until the vigorous effervescence slackened (5–7 min). The cooled melt was extracted several times with boiling water and the residue recrystallized (AcOH aq, charcoal) to give the ester (0·50 g, 26%) as dark, yellow-brown needles m.p. 139–142°. The dark colour could not be removed by recrystallization, but by passing a benzene solution through a column of acid-washed, methanol-deactivated alumina, the m.p. could be raised to 143–145°, undepressed by admixture with a sample prepared as in (A).

Reduction of methyl 3′,6-dinitrodiphenylamine-2-carboxylate, characterization of the diaminodiphenylamine and its cyclization

The diphenylamine ester was hydrogenated over PtO_2. Acetylation of the residue, after removal of the solvent in a stream of N_2, gave methyl 3′,6-*diacetamidodiphenylamine-2-carboxylate* which recrystallized (AcOH aq) as pale yellow plates m.p. 208–210° (Found: C, 62·9; H, 5·7; N, 11·6. $C_{18}H_{19}N_3O_4$ requires: C, 63·4; H, 5·6; N, 12·3%).

In the usual way, the dinitrodiphenylamine ester (2 g) was hydrogenated and a solution of the product in nitrobenzene (250 cc) then refluxed for 30 hr. The nitrobenzene was removed under red. press. and a benzene solution of the oily residue adsorbed on a column (2 × 30 cm) of acid-washed, methanol-deactivated alumina. Development of the column with benzene removed a deep red band

[15] P. J. Culhane, *Organic Syntheses* Coll Vol. I, 125.
[16] R. W. Stoughton and R. Adams, *J. Amer. Chem. Soc.* **54**, 4426 (1932).

and elution with ether stripped an orange band. Evaporation of the latter gave methyl 8-aminophenazine-1-carboxylate (0·45 g, 28%) which recrystallized (benzene–pet. ether) as red needles m.p. 188°. The m.p. was not depressed by a sample of the ester obtained by the alternative route described above; the ester from the two sources also had identical IR spectra (KCl disc) and travelled at the same rate on paper chromatography in three different solvents (A, B, C).

The benzene eluate of the red band was evaporated to small bulk and run through a second similar alumina column. Evaporation of the solvent and two crystallizations (EtOH aq) of the residue gave *methyl 6-aminophenazine-1-carboxylate* (40 mg, 2·5%) as bright red needles, m.p. 144° (Found: C, 66·5; H, 4·4; N, 16·5. $C_{14}H_{11}N_3O_2$ requires: C, 66·4; H, 4·3; N, 16·6%).

The ester (22 mg) in N NaOH (3 cc) was heated at 100° for 30 min. Acidification of the filtered solution with acetic acid and recrystallization (EtOH aq) of the precipitate gave 6-aminophenazine-1-carboxylic acid (16 mg, 77%), as fluffy purple needles m.p. 305–307° (Found: C, 64·8; H, 3·7; N, 17·3. $C_{13}H_9N_3O_2$ requires: C, 65·3; H, 3·75; N, 17·6%). Decarboxylation of this acid by heating with copper powder in quinoline was very rapid (10 min) and resulted in a change in colour from deep purple to red. The product was isolated by chromatography on alumina with benzene and, subsequently, ether as solvents; it had m.p. 173–176°, unchanged by admixture with 1-aminophenazine with which identity was confirmed by paper chromatography in 3 different solvents (A, B, C).

Reduction of 3',6-dinitrodiphenylamine-2-carboxylic acid and cyclization of the diaminodiphenylamine

The crude acid (1·45 g) was hydrogenated over Pd–charcoal as far as possible, a colourless solution never being obtained. A solution of the product in nitrobenzene (112 cc) was refluxed for 12 hr. The bulk of the nitrobenzene was removed under red. press., the residual solution diluted with benzene and filtered. The precipitate (0·65 g) was dissolved in 96% ethanol (2·1 l.) and adsorbed on a column of alumina (3·5 × 21 cm). Development with a large volume of ethanol carried through a diffuse band, the progress of which could be followed by its intense green fluorescence in UV light. Evaporation of the solvent and recrystallization (nitrobenzene) of the residue gave brown-yellow needles m.p. above 350°. This product was shown to be 1,8-diaminoacridone by comparison (paper chromatography in solvents A, B, and D and IR spectra of KCl discs) with a sample prepared by the method of Goldberg and Kelly.[18]

Elution of the column with methanol, followed by 5% acetic acid in ethanol, removed 2-aminophenazine-9-carboxylic acid which was identified by paper chromatography (solvents A, B, D).

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