688. *Syntheses of Polycyclic Systems. Part I. A New Synthesis of Phenanthridine and Phenanthridine Derivatives.*

By E. A. Braude and J. S. Fawcett.

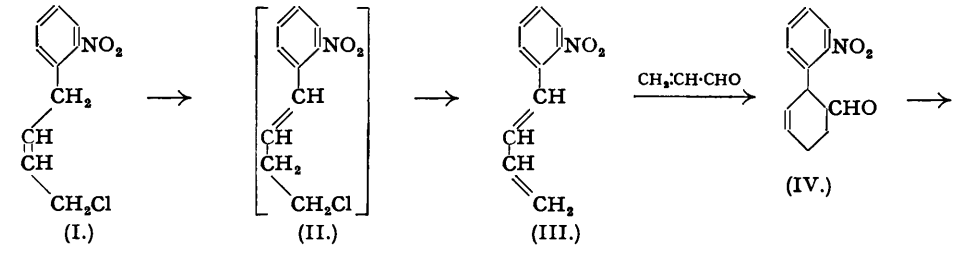
A novel synthesis of phenanthridine and phenanthridine derivatives is described. *o*-Nitrophenylbutadiene (III), prepared by the action of diazotised *o*-nitroaniline on butadiene and treatment of the resulting chlorobutene (I) with alcoholic potassium hydroxide, reacts with acraldehyde to give 2-formyl-1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl (IV). This undergoes catalytic hydrogenation and simultaneous dehydration to give the octahydrophenanthridine (VIII), which on dehydrogenation by selenium affords phenanthridine in an overall yield of 15% based on *o*-nitroaniline.

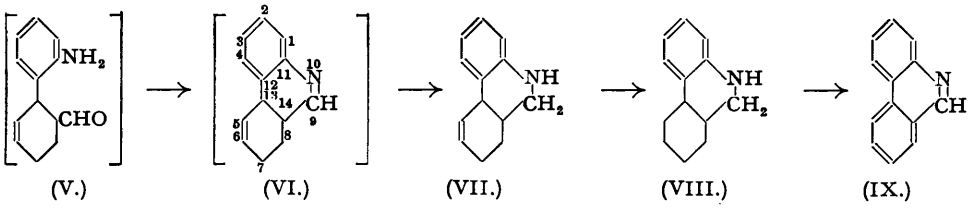
o-Nitrophenylbutadiene similarly reacts with acrylic acid to give 1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl-2-carboxylic acid (X) and with maleic anhydride to give the adduct (XIV). Reduction of the nitro-group in (X) followed by dehydration affords the tetrahydrophenanthridone (XII), which is dehydrogenated to phenanthridone. The acid (X) and the adduct (XIV) can also be converted directly into phenanthridone by selenium.

Although a variety of synthetical routes to phenanthridine and its derivatives have been described (for a summary, see Theobald and Schofield, *Chem. Reviews*, 1950, **46**, 171), many of the methods hitherto available are either restricted in scope or involve relatively inaccessible intermediates. Moreover, few of the existing methods are readily adaptable to the synthesis of hydrophenanthridine structures such as occur in certain groups of alkaloids and other natural products. A new synthetical approach is now illustrated with respect to the parent base and some of its simple derivatives. The method resembles some of the earlier ones in that it involves the cyclisation of a diphenyl derivative carrying an unsaturated carbon and nitrogen function, respectively, in the *o*- and the *o*′-position : it differs from earlier methods in the preparation of the diphenyl derivatives and in the choice of the *oo*′-substituents.

The key intermediate in the present synthesis is *o*-nitrophenylbutadiene (III), which is prepared in high yield by the action of *o*-nitrobenzenediazonium chloride on butadiene in the presence of cupric chloride and treatment of the resulting 1-chloro-4-*o*-nitrophenylbut-2-ene (I) with alcoholic potassium hydroxide. Analogous reactions have been carried out with nitrobenzene- and several other diazonium chlorides (Meerwein, Bückner, and Emster, *J. pr. Chem.*,

1939, 152, 237; Koelsch and Bockelheide, *J. Amer. Chem. Soc.*, 1944, **66,** 412; Bergmann and Schapiro, *J. Org. Chem.*, 1947, **12,** 57; L'Ecuyer, Turcotte, *et al.*, *Canad. J. Res.*, 1947, **25,** 575; 1948, **26,** 70; Rai and Mathur, *J. Indian Chem. Soc.*, 1947, **24,** 383, 413; Coyner and Ropp, *J. Amer. Chem. Soc.*, 1948, **70,** 2283; 1950, **72,** 3960). The initial 1 : 4-addition reaction





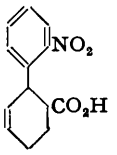
almost certainly takes place by homolytic decomposition of the diazonium salt into aryl radicals and chlorine atoms (cf. Koelsch and Bockelheide, *loc. cit.*). The subsequent dehydrochlorination is probably preceded by a rearrangement of the unconjugated but-2-ene (I) to the conjugated but-1-ene (II), which then undergoes a 1 : 2-elimination reaction. The prototropic change will be catalysed by the alkali and facilitated by the strongly electron-attracting nitro-substituent.

The diene readily undergoes a Diels–Alder reaction with acraldehyde, reaction being substantially complete after 6 hours at 80°. The condensation of phenylbutadiene with acraldehyde requires considerably more drastic conditions (Lehmann and Paasche, *Ber.*, 1935, **68,** 1146; Lehmann, *ibid.*, 1936, **69,** 631), and *o*-tolylbutadiene fails to react (Braude and Fawcett, forthcoming paper), so the Diels–Alder reaction is strongly facilitated by an electron-attracting substituent. The structure of the resulting 2-formyl-1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl (IV), a low-melting solid which was characterised by a semicarbazone and a 2 : 4-dinitrophenylhydrazone, follows from its conversion into phenanthridine (see below). The orientation of the addition reaction corresponds to that observed with the reaction between phenylbutadiene and acraldehyde (Meek, Lorenzi, and Cristol, *J. Amer. Chem. Soc.*, 1949, **71,** 1830) and none of the possible alternative 3-formyl derivative was isolated. The nitro-aldehyde (IV) readily undergoes catalytic hydrogenation in the presence of Raney nickel, and the resulting amino-aldehyde (V) undergoes spontaneous intramolecular dehydration and further hydrogenation, giving 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthridine (VIII) which was prepared by Kruber (*Ber.*, 1939, **72,** 771) by reduction of phenanthridone with sodium and alcohol. Octahydrophenanthridine was characterised as the picrate and the benzoyl derivative. When the catalytic reduction of the nitro-aldehyde (IV) in the presence of Raney nickel was interrupted at an intermediate stage, a hexahydrophenanthridine was obtained which exhibited the ultra-violet light absorption expected for (VII).

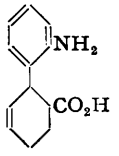
When heated with selenium at 330°, octahydrophenanthridine was converted in good yield into phenanthridine (IX). The overall yield of the five-step synthesis is 15%, based on *o*-nitroaniline. Dehydrogenation of octahydrophenanthridine by selenium at 250° afforded a low yield of a tetrahydrophenanthridine, which was isolated as the picrate and was not identical with the 5 : 6 : 7 : 8-tetrahydro-derivative obtained by Hollingworth and Petrow (*J.*, 1948, 1537; cf. Kenner, Ritchie, and Statham, *J.*, 1937, 1169).

The reaction between *o*-nitrophenylbutadiene and acrylic acid proceeds somewhat less readily than the reaction with acraldehyde, but as in the case of phenylbutadiene (Meek, Lorenzi, and Cristol, *J. Amer. Chem. Soc.*, 1949, **71,** 1830; Ropp and Coyner, *ibid.*, p. 1832; Alder, Vagt, and Vogt, *Annalen*, 1949, **565,** 135) only the product with the desired orientation, in this case 1 : 2 : 3 : 4-tetrahydro-2′-nitrodiphenyl-2-carboxylic acid (X), is obtained. The constitution of the acid, which was isolated in *cis*- and *trans*-forms each characterised by a

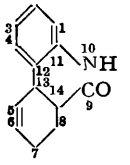
benzylamine salt, is proved by its ultra-violet light absorption properties and by the reactions described below.



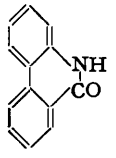
(X.)



(XI.)



(XII.)



(XIII.)

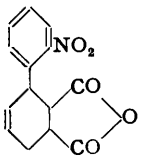
The conversion of the nitro-acid (X) into phenanthridone was effected by three different routes :

(i) Reduction of the nitro-group by catalytic hydrogenation in the presence of Raney nickel afforded the amino-acid (XI). In contrast to 2'-aminodiphenyl-2-carboxylic acid, which undergoes spontaneous dehydration to phenanthridone (Graebe and Wander, *Annalen*, 1893, **276**, 245), the tetrahydro-acid (XI) sublimes unchanged and is not cyclised on treatment with hot potassium hydroxide solution. Dehydrogenation and cyclisation to phenanthridone (XIII) was, however, readily effected by selenium at 250°.

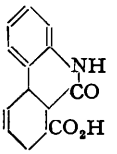
(ii) Reduction of the nitro-acid (X) with boiling alkaline sodium dithionite (hydrosulphite) solution afforded 7 : 8 : 13 : 14-tetrahydrophenanthridone (XII), which was dehydrogenated to phenanthridone by selenium at 250°. It is noteworthy that in this reaction cyclisation occurs under alkaline conditions; since the amino-acid (XI) is unaffected by strong alkali, it must be presumed that cyclisation takes place at an intermediate reduction stage of the nitro-group.

(iii) The nitro-acid (X) can also be converted directly into phenanthridone, though necessarily in lower yield, by heating it with selenium at 250°. Under these conditions, dehydrogenation of the *cyclo*hexenyl group and reduction of the nitro-group take place simultaneously, the acid acting as hydrogen-donor as well as hydrogen-acceptor. Since only 4 atoms of hydrogen per molecule are made available in the dehydrogenation, whereas 6 atoms are required for complete reduction of the nitro-group, the 50% yield of phenanthridone obtained in the reaction represents 75% of the theoretical.

A further route to phenanthridone is provided by the addition of *o*-nitrophenylbutadiene to maleic anhydride to give the adduct (XIV) which is converted into phenanthridone when



(XIV.)



(XV.)

heated with selenium at 250°. The adduct (XIV) is also hydrolysed by hot alkali to the corresponding tetrahydro-dicarboxylic acid, which undergoes simultaneous reduction and cyclisation on treatment with sodium dithionite, giving the tetrahydrophenanthridonecarboxylic acid (XV).

Each of the three components—nitroamine, diene, and dienophile—employed in the present synthesis is readily capable of structural variation, and further applications will be described later.

Experimental.

(M. p.s are uncorrected. Light-absorption data refer to ethanol solutions unless otherwise stated.)

1-*Chloro*-4-o-*nitrophenylbut*-2-*ene*.—*o*-Nitroaniline (140 g.) was warmed with concentrated hydrochloric acid (240 ml.) and water (200 ml.) and then cooled in an ice-bath. Sodium nitrite (70 g.) in water (120 ml.) was slowly added during 1 hour at 0°. This diazotised solution was kept ice-cold while it was gradually added to a stirred mixture of butadiene (120 ml.), acetone (1 l.), sodium acetate solution (80 g. in 100 ml. of water), and cupric chloride solution (30 g. in 50 ml. of water), cooled in ice–salt. The reaction mixture was stirred overnight. The oil which separated was extracted with ether, the extract washed with water and dried, and the ether evaporated, to give the crude 1-*chloro*-4-o-*nitrophenylbut*-2-*ene* (160 g.), a small quantity of which was purified by fractional distillation, b. p. 126°/5 × 10^{-3} mm., n_D^{20} 1·5653 (Found : N, 6·4. $C_{10}H_{10}O_2NCl$ requires N, 6·6%).

1-o-*Nitrophenylbuta*-1 : 3-*diene*.—The crude 1-chloro-4-*o*-nitrophenylbut-2-ene (160 g.) was dissolved in methanol (400 ml.), and a solution of potassium hydroxide (110 g.) in methanol (600 ml.) added to the stirred solution, the temperature being kept between 20° and 30° by occasional cooling. The brown crystalline product was filtered off, washed with water, and, after treatment with charcoal, crystallised from methanol, to give pale yellow needles of 1-o-*nitrophenylbuta*-1 : 3-*diene* (90 g.), m. p. 67° (Found :

C, 68·6; H, 5·4; N, 7·8. $C_{10}H_9O_2N$ requires C, 68·6; H, 5·1; N, 8·0%). Light absorption: $\lambda_{max.}$ 2580, 2650, 2810, and 3350 A.; ε = 21,500, 20,500, 17,500, and 4300, respectively.

2-*Formyl*-1 : 2 : 3 : 4-*tetrahydro*-2′-*nitrodiphenyl*.—The above butadiene (24 g.) was refluxed with acraldehyde (12 g.) for 5 hours. The excess of aldehyde was distilled out, and the product distilled under high vacuum. A small amount of unchanged diene (*ca.* 1 g.) sublimed first and then the *diphenyl derivative* (17 g.) distilled as a yellow-orange liquid, b. p. 100° (bath)/10^{-5} mm., which solidified on cooling and crystallised from light petroleum (b. p. 60—80°) as colourless rods, m. p. 46° (Found: C, 67·5; H, 5·6; N, 6·1. $C_{13}H_{13}O_3N$ requires C, 67·5; H, 5·7; N, 6·1%). Light absorption: $\lambda_{max.}$ 2510, 2580, and 2800 A.; ε = 4400, 4500, and 4900, respectively. The *semicarbazone* separated from ethanol as colourless crystals, m. p. 184° (Found: C, 58·5; H, 5·7; N, 19·75. $C_{14}H_{16}O_3N_4$ requires C, 58·3; H, 5·6; N, 19·4%). The 2 : 4-*dinitrophenylhydrazone* separated from ethyl acetate in yellow crystals, m. p. 161° (Found: C, 55·2; H, 4·3; N, 17·1. $C_{19}H_{17}O_6N_5$ requires C, 55·5; H, 4·15; N, 17·0%). Light absorption in chloroform: Maximum at 3600 A.; ε = 21,600.

5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-*Octahydrophenanthridine*.—The foregoing aldehyde (8 g.) in ethanol (300 ml.) was hydrogenated at 20°/1 atm. in the presence of Raney nickel (0·5 g.). After 8 hours, 3·9 mols. of hydrogen had been absorbed. Filtration and evaporation of the solution gave 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-octahydrophenanthridine (4 g.), which, crystallised from aqueous ethanol, had m. p. 72° (Found: C, 83·5; H, 9·2; N, 7·3. Calc. for $C_{13}H_{17}N$: C, 83·4; H, 9·1; N, 7·5%); Kruber (*Ber.*, 1939, **72**, 771) gives m. p. 74°. Light absorption: $\lambda_{max.}$ 2510, 2560, and 3040 A.; ε = 7800, 7100, and 2200, respectively. The benzoyl derivative crystallised from aqueous methanol as colourless needles, m. p. 142° (Found: C, 82·5; H, 7·4; N, 4·85. Calc. for $C_{20}H_{21}ON$: C, 82·45; H, 7·2; N, 4·8%); Kruber (*loc. cit.*) gives m. p. 140°. The *picrate* crystallised from ethanol as orange-yellow prisms, m. p. 167° (Found: C, 55·0; H, 4·85; N, 13·3. $C_{19}H_{20}O_7N_4$ requires C, 54·8; H, 4·8; N, 13·5%).

7 : 8 : 9 : 10 : 13 : 14-*Hexahydrophenanthridine*.—The diphenyl-aldehyde (5·5 g.) in ethanol (200 ml.) was hydrogenated at atmospheric pressure in the presence of Raney nickel (0·5 g.). The hydrogenation was stopped after 3 hours when 1·85 l. (3·2 mols.) of hydrogen had been absorbed. Filtration and concentration of the solution gave a pale yellow, viscous oil (4·5 g.). Distillation of the product at 10^{-5} mm. gave a colourless sublimate of 7 : 8 : 9 : 10 : 13 : 14-*hexahydrophenanthridine* (2·5 g.), which separated from methanol as crystals, m. p. 104—105° (Found: C, 84·45; H, 8·25; N, 7·4. $C_{13}H_{15}N$ requires C, 84·3; H, 8·1; N, 7·6%). Light absorption: $\lambda_{max.}$ 2510, 2560, and 3040 A.; ε = 6400, 7200, and 2500, respectively.

Phenanthridine and Tetrahydrophenanthridine.—(*a*) 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-Octahydrophenanthridine (1 g.) was heated with selenium (3 g.) at 250° for ½ hour and then at 330° for 12 hours. On cooling, the residue was extracted with ether. Evaporation of the ether and sublimation of the product gave phenanthridine (0·9 g.), m. p. 105—106°, undepressed on admixture with an authentic specimen, kindly provided by Dr. A. G. Caldwell.

(*b*) 5 : 6 : 7 : 8 : 9 : 10 : 13 : 14-Octahydrophenanthridine (1 g.) was heated with selenium (3 g.) at 250° for 3 hours. Extraction with ether gave a mixture of unchanged octahydrophenanthridine and a tetrahydrophenanthridine, isolated as a *picrate*, which crystallised from ethanol as yellow needles, m. p. 210—212° (Found: C, 55·5; H, 4·0; N, 13·6. $C_{19}H_{16}O_7N_4$ requires C, 55·4; H, 3·9; N, 13·6%). On admixture with the picrate, m. p. 211—213°, prepared from an authentic sample of 5 : 6 : 7 : 8-tetrahydrophenanthridine kindly provided by Dr. V. Petrow (cf. Hollingworth and Petrow, *J.*, 1948, 1537), the m. p. was depressed to 205—207°.

1 : 2 : 3 : 4-*Tetrahydro*-2′-*nitrodiphenyl*-2-*carboxylic Acid*.—(*a*) *o*-Nitrophenylbutadiene (20 g.) and acrylic acid (20 g.) were refluxed together for 18 hours. Excess of acrylic acid was distilled off, and the residue dissolved in ether. The ethereal extract was shaken twice with sodium carbonate solution. Acidification of the carbonate solution gave the (? trans-)*acid* (22 g.), which crystallised from methanol as colourless prisms, m. p. 141° (Found: C, 63·3; H, 5·3; N, 5·9. $C_{13}H_{13}O_4N$ requires C, 63·2; H, 5·3; N, 5·7%). Light absorption: $\lambda_{max.}$ 2510, inflection at 2900 A.; ϵ = 6700 and 2500, respectively. The *benzylamine* salt crystallised from carbon tetrachloride as fine rods, m. p. 120° (Found: C, 67·4; H, 6·4; N, 7·6. $C_{20}H_{22}O_4N_2$ requires C, 67·8; H, 6·25; N, 7·9%). The acid (m. p. 141°) was recovered unchanged after 4 hours in boiling 0·1% sodium hydroxide solution. It was decomposed when heated with 10% sodium hydroxide solution.

(*b*) In one experiment, *o*-nitrophenylbutadiene (6 g.) and acrylic acid (4 g.) were refluxed together for 12 hours. The mixture was extracted with sodium carbonate solution, which on acidification gave an isomeric (?cis-)*acid* (5·6 g.) which, crystallised from aqueous methanol, had m. p. 122—123° (Found: C, 62·9; H, 5·3; N, 6·1%). Light absorption in ethanol: $\lambda_{max.}$ 2510, 2560, and 2900 A.; ϵ = 4800, 4800, and 1850, respectively. The *benzylamine* salt crystallised from carbon tetrachloride and had m. p. 125—126°, depressed to 105° on admixture with the isomeric salt obtained as in (*a*) (Found: N, 7·9%).

2′-*Amino*-1 : 2 : 3 : 4-*tetrahydrodiphenyl*-2-*carboxylic Acid*.—The nitro-acid (5·8 g.) in ethanol (200 ml.) was shaken in an atmosphere of hydrogen in the presence of Raney nickel until 1700 ml. (3 mols.) of hydrogen (at 20°/748 mm.) had been absorbed. Filtration and concentration of the solution gave the *amino-acid* (3·5 g.) which crystallised from methanol as rods, m. p. 175—177° (Found: C, 71·5; H, 6·5; N, 6·7. $C_{13}H_{15}O_2N$ requires C, 71·9; H, 6·9; N, 6·45%). Light absorption in *cyclo*hexane: $\lambda_{max.}$ 2510, inflection at 2560 A.; ϵ = 15,500 and 15,000, respectively. This amino-acid failed to give a picrate and was not cyclised when heated at 200° or refluxed with 10% sodium hydroxide solution.

Phenanthridone and 7 : 8 : 13 : 14-*Tetrahydrophenanthridone*.—(*a*) The nitro-acid (1 g.) and selenium (2 g.) were heated together at 150° for 1 hour. The temperature was gradually raised to 300°, and heating continued for a further hour. On cooling, the residue and sublimate were ground to a fine powder

and extracted with chloroform (Soxhlet). Evaporation of the solution gave phenanthridone (0·35 g.), which crystallised from ethanol as needles, m. p. 290—293°, undepressed on admixture with an authentic specimen, prepared by Smith's method (*J. Amer. Chem. Soc.*, 1948, **70**, 320).

(*b*) The amino-acid (70 mg.) and selenium (300 mg.) were heated in a sealed tube at 250° for 1 hour and then at 330° for 2 hours. Extraction of the mixture with hot methanol gave phenanthridone as pale yellow needles (30 mg.), m. p. 285°, undepressed on admixture with an authentic specimen.

(*c*) The nitro-acid (1 g.), sodium dithionite (3·5 g.), and 10% sodium hydroxide solution (20 ml.) were refluxed together for 30 minutes. On cooling and acidification with acetic acid, 7 : 8 : 13 : 14-*tetrahydrophenanthridone* (0·5 g.) was obtained, which crystallised from methanol as needles, m. p. 194—195° (Found : C, 78·3; H, 6·6; N, 6·7. $C_{13}H_{13}ON$ requires C, 78·4; H, 6·6; N, 7·0%). Light absorption : $\lambda_{max.}$ 2510 and 2560 A., ϵ = 9800 and 9100, respectively.

7 : 8 : 13 : 14-Tetrahydrophenanthridone (1 g.) and selenium (1 g.) were heated together at 250° for 1 hour. Extraction of the mixture with hot methanol gave phenanthridone (0·4 g.), m. p. 288°, undepressed on admixture with an authentic specimen.

1 : 2 : 3 : 4-*Tetrahydro-2'-nitrodiphenyl-2* : 3-*dicarboxylic Anhydride and Acid.*—1-*o*-Nitrophenylbutadiene (4 g.), maleic anhydride (2·5 g.), and benzene (5 ml.) were refluxed together for 15 minutes. On cooling, the above *anhydride* (6 g.) separated, and crystallised from ethyl acetate as prisms, m. p. 154° (Found : C, 61·4; H, 4·1; N, 5·1. $C_{14}H_{11}O_5N$ requires C, 61·5; H, 4·05; N, 5·1%). Light absorption in chloroform : $\lambda_{max.}$ 2570, 2650, and 2800 A., inflection 2500 A.; ϵ = 5700, 5300, 4100, and 4900, respectively. The anhydride (0·5 g.) was dissolved in hot 10% sodium hydroxide solution (20 ml.); acidification of the solution gave the *acid* (0·48 g.), which crystallised from methanol as colourless prisms, m. p. 215° (Found : C, 57·8; H, 4·6; N, 5·2. $C_{14}H_{13}O_6N$ requires C, 57·7; H, 4·5; N, 4·8%).

When the anhydride (1 g.) was heated with selenium (3 g.) at 200° for 2 hours and then at 250° for 1 hour, phenanthridone (0·3 g.) was obtained as a white sublimate, m. p. 285°, undepressed on admixture with an authentic specimen.

Reduction of the Foregoing Anhydride by Sodium Dithionite.—The above anhydride (2 g.) and sodium dithionite (7 g.) were dissolved in 10% aqueous sodium hydroxide (40 ml.). The solution was refluxed for 30 minutes and then neutralised by addition of acetic acid. On cooling, the product separated in fine colourless needles (0·95 g.). It could not be crystallised, but was purified by precipitation with acid from alkaline solution, and had m. p. 216° (Found : C, 68·5; H, 5·6; N, 5·6. $C_{14}H_{13}O_3N$ requires C, 69·15; H, 5·4; N, 5·75%). Light absorption : $\lambda_{max.}$ 2510, inflection at 2560 A.; ϵ = 11,400 and 11,000, respectively. The product dissolved in sodium carbonate solution with slow evolution of carbon dioxide. It was not diazotised by sodium nitrite solution and is formulated as 7 : 8 : 13 : 14-*tetrahydrophenanthridone*-8-*carboxylic acid.*

The authors of this and the following paper thank the Department of Scientific and Industrial Research for a Maintenance Grant (J. S. F.).

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[*Received, May 18th*, 1951.]