

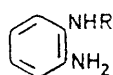
Synthesis of Quinoxalinones by the Reaction of *o*-Phenylenediamines with Dimethyl Acetylenedicarboxylate

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The reaction of *N*-monosubstituted *o*-phenylenediamines with dimethyl acetylenedicarboxylate gives 1-substituted 3-(ethoxycarbonylmethylene)-3,4-dihydroquinoxalin-2(1*H*)-ones. Hydrolysis and decarboxylation of these products is accompanied by rearrangement to the 1-substituted 3-methylquinoxalin-2-ones. In the case of the product derived from 7-amino-2-methylindoline, the intermediate 3-methylene compound was obtained.

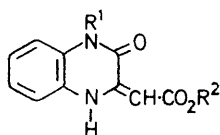
SEVERAL possible products may be envisaged for the reaction between *o*-phenylenediamines (1) and acetylenedicarboxylates, notably quinoxalin-2-ones (2) or benzodiazepinones (3), or isomers or tautomers of the structures shown. We report the results of a reinvestigation of the reaction with *o*-phenylenediamine itself, and studies on the reactions of some *N*-monosubstituted derivatives.

As long ago as 1900, the product from *o*-phenylenediamine and diethyl acetylenedicarboxylate was formulated as the imine tautomer (4) of a quinoxaline.¹



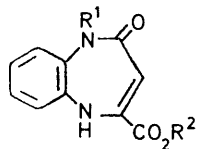
(1)

- a ; R = H
b ; R = CH₂·CH=CH₂
c ; R = Pr

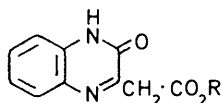


(2)

- a ; R¹ = H, R² = Et
b ; R¹ = H, R² = Me
c ; R¹ = CH₂·CH=CH₂, R² = Me
d ; R¹ = Pr, R² = Me

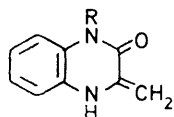


(3)

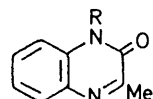


(4)

- a ; R = Et
b ; R = Me



(5)



(6)

- a ; R = H
b ; R = CH₂·CH=CH₂
c ; R = Pr

Iwanami,² however, found that the product showed i.r. absorption at 1690 (ester C=O str.), 1645 (amide C=O str.), and 818 cm⁻¹ (trisubstituted C=C), and formulated it as the methylenequinoxalin-2-one (2a). Hydrolysis and

decarboxylation gave a compound showing i.r. absorption at 1665 (amide C=O str.) and 895 cm⁻¹ (assigned to the methylene group), and formulated as (5). We have confirmed that both the reaction of *o*-phenylenediamine with dimethyl acetylenedicarboxylate, and the subsequent hydrolysis and decarboxylation, give products with i.r. spectra similar to those reported by Iwanami. The ¹H n.m.r. spectrum of the adduct showed no signals attributable to a saturated methylene group, confirming its structure as (2b) rather than (4b) (the signals for the olefinic proton could not be resolved from those due to the aromatic protons). On the other hand, the spectrum of the product from hydrolysis and decarboxylation showed no signals assignable to olefinic protons, but a singlet (3H) at τ 7.6. The latter compound is thus the imine (6a), rather than the enamine (5).

The reaction of acetylenedicarboxylates with *N*-allyl-*o*-phenylenediamine (1b) could give products by reactions involving the allyl substituent. Two groups have reported the preparation of compound (1b) by reduction of *N*-allyl-2-nitroaniline, with Raney nickel³ or tin(II) chloride and hydrochloric acid.⁴ In our hands reduction with Raney nickel and hydrazine gave *N*-propyl-*o*-phenylenediamine (1c) and with tin(II) chloride and hydrochloric acid a mixture of products was obtained, from which 7-amino-2-methylindoline (7) was isolated in 15% yield. The structure of the indoline (7) was established by its ¹H n.m.r. spectrum, and by dehydrogenation to 7-amino-2-methylindole (8). The reduction of *N*-allyl-2-nitroaniline to *N*-allyl-*o*-phenylenediamine (1b) was achieved, in good yield, with iron and ammonium chloride. On treatment with hot, concentrated hydrochloric acid, the *N*-allyl compound (1b) gave 7-amino-2-methylindoline (7), together with *o*-phenylenediamine. The formation of the indoline (7) probably involves an acid-catalysed Claisen-type rearrangement (*cf.* refs. 5—7). On treatment with hot concentrated hydrochloric acid, *N*-allyl-2-nitroaniline (9) gave *o*-nitroaniline, with only a trace of 2-methyl-7-nitroindoline (10), and also traces of compounds whose spectra suggested that they were the indoles (11) and (12).

The only product isolated from the reaction of *N*-allyl-*o*-phenylenediamine (1b) with dimethyl acetylenedicarboxylate had an n.m.r. spectrum (see Experimental section) which clearly revealed the presence of the intact

¹ S. Ruhemann and H. E. Stapleton, *J. Chem. Soc.*, 1900, 77, 239.

² Y. Iwanami, *Nippon Kagaku Zasshi*, 1961, 82, 778.

³ V. C. Barry, J. G. Belton, N. F. O'Sullivan, and D. Twomey, *J. Chem. Soc.*, 1956, 893.

⁴ B. W. Ashton and H. Suschitzky, *J. Chem. Soc.*, 1957, 4559.

⁵ C. D. Hurd and W. W. Jenkins, *J. Org. Chem.*, 1957, 22, 1418.

⁶ A. R. Bader, R. J. Bridgewater, and P. R. Freeman, *J. Amer. Chem. Soc.*, 1961, 83, 3319.

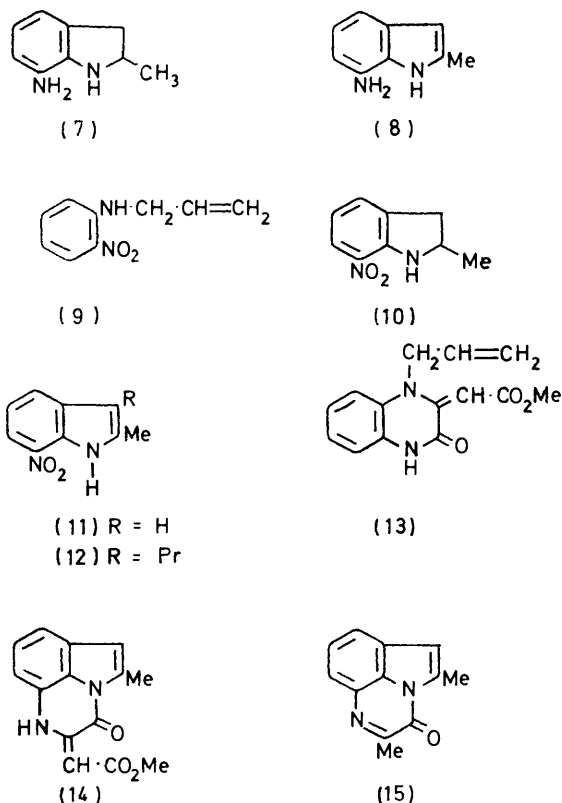
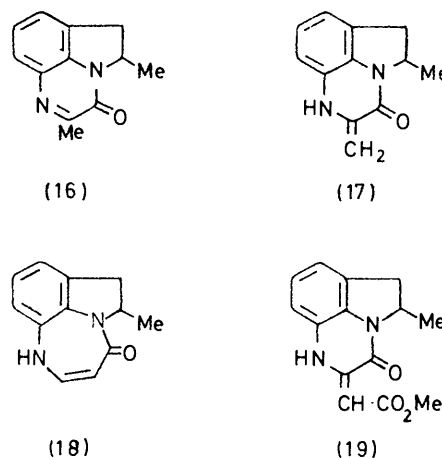
⁷ M. Schmid, H. J. Hansen, and H. Schmid, *Helv. Chim. Acta*, 1973, 56, 105.

allyl group but did not distinguish between the quinoxaline (2c) or benzodiazepine (3; R = allyl) structures, nor between the possible isomers of these structures. However, hydrolysis and decarboxylation gave a single product, showing a singlet (3H) at τ 7.5, which was clearly the quinoxaline (6b). The initial adduct was therefore a quinoxalinone with the structure (2c), rather than its isomer (13) whose decarboxylated hydrolysis product could not rearrange to a methyl imine.

On reaction with dimethyl acetylenedicarboxylate, both *N*-propyl-*o*-phenylenediamine (1c) and 7-amino-2-methylindole (8) gave products, (2d) and (14), respectively, analogous to those from *N*-allyl-*o*-phenylenediamine (1b); hydrolysis and decarboxylation of these products gave compounds, (6c) and (15), showing a singlet (3H) at τ 7.5 in their n.m.r. spectra.

The product from the reaction of 7-amino-2-methylindoline (7) with dimethyl acetylenedicarboxylate, followed by hydrolysis and decarboxylation, did not show an n.m.r. signal attributable to the methyl group of

when the n.m.r. spectrum was re-recorded after 3 months; the signals due to the olefinic protons had been partially replaced by a singlet at τ 7.7, showing that slow rearrangement to compound (16) was occurring.



the imine tautomer (16). Instead broadened singlets (each 1H), at τ 4.9 and 5.8, were observed. Both the methylenequinoxaline (17) and the diazepinoindole (18) could have given this type of spectrum, but in the latter case larger coupling constants for the olefinic protons would have been expected, giving rise to doublets. Confirmation of the assignment of structure (17) came

* This compound was first described in ref. 3, but was not fully characterised. In ref. 4, analytical data were given, but the n.m.r. spectrum was not available; it is thus not possible to be sure whether the compound reported in ref. 4 was *N*-allyl-*o*-phenylenediamine (1b) or the indoline (7).

EXPERIMENTAL

*Reduction of N-Allyl-*o*-nitroaniline.*—(a) *With Raney nickel and hydrazine.*³ Raney nickel (3.0 g) was added in small portions to a warm solution of *N*-allyl-*o*-nitroaniline (25 g, 0.14 mol) and hydrazine hydrate (21 g, 0.42 mol) in ethanol (250 ml). After 2 h, further Raney nickel was added and the mixture was heated on a water-bath and filtered. The solvent was evaporated off and the black residue was distilled, to give *N*-propyl-*o*-phenylenediamine³ (1c) (17 g, 81%), b.p. 144–148° at 2 mmHg, τ (CCl₄) 3.1–3.7 (4H, m, ArH), 6.9br (3H, exch., NH, NH₂), 7.1 (2H, t, NH-CH₂), 8.45 (2H, m, CH₂-CH₂-CH), and 9.0 (3H, t, CH₃) (Found: C, 72.15; H, 9.3; N, 18.35%; *M*⁺, 150. Calc. for C₉H₁₄N₂: C, 72.0; H, 9.4; N, 18.65%; *M*, 150).

(b) *With iron and ammonium chloride.* *N*-Allyl-*o*-nitroaniline (100 g, 0.56 mol) was added in small portions to a boiling, stirred mixture of reduced iron (100 g, 1.79 mol) and ammonium chloride (12 g, 0.22 mol) in water (120 ml). The mixture was heated under reflux during 1 h, cooled, filtered, and extracted with chloroform. The extract was dried and evaporated, and the black residue was distilled to give *N*-allyl-*o*-phenylenediamine (1b)* (55 g, 66%), b.p. 88–92° at 0.3 mmHg, τ (CCl₄) 3.4 (4H, m, ArH), 4.2 (1H, m, CH=CH₂), 4.8 (2H, m, CH=CH₂), 6.45 (2H, m, NH-CH₂), and 6.8 (3H, s, exch., NH, NH₂) (Found: C, 72.6; H, 8.35; N, 18.6%; *M*⁺, 148. C₉H₁₂N₂ requires C, 72.9; H, 8.2; N, 18.9%; *M*, 148).

(c) *With tin(II) chloride and hydrochloric acid.*⁴ *N*-Allyl-*o*-nitroaniline (10 g) was added to a mixture of concentrated hydrochloric acid (200 ml) and tin(II) chloride (40 g). The solution was heated under reflux overnight, cooled, basified, filtered, and extracted with chloroform. The extract was dried and evaporated and the black residue distilled to give 7-amino-2-methylindoline (7) (1.5 g, 15%), b.p. 102–106° at 0.5 mmHg, identical (spectra) with the compound described below.

7-Amino-2-methylindoline and -indole.—A solution of *N*-allyl-*o*-phenylenediamine (50 g) in concentrated hydrochloric acid (250 ml) was heated under reflux during 24 h, cooled, basified with concentrated aqueous ammonia, and extracted with chloroform. The extract was dried and evaporated and the black residue was distilled, to give *o*-phenylenediamine (9.8 g, 29%), b.p. 82–86° at 0.5 mmHg,

and 7-amino-2-methylindoline (7) (23 g, 46%), b.p. 102—106° at 0.5 mmHg, τ (CCl₄) 3.5 (3H, m, ArH), 6.45 (1H, m, 2-H), 6.7 (3H, s, exch., NH, NH₂), 7.1 and 7.2 (2H, overlapping q, 3-H), and 9.0 (3H, d, CH₃) (Found: C, 72.4; H, 7.9; N, 18.8%; M^+ , 148. C₉H₁₂N₂ requires C, 72.9; H, 8.2; N, 18.9%; M , 148).

7-Amino-2-methylindoline (20 g) and 5% palladium-charcoal (2.0 g) were heated at 200° during 15 min. The cooled product was extracted with ether, the extract was evaporated, and the black residue was distilled to give 7-amino-2-methylindole (8) (11.8 g, 60%), b.p. 180—182° at 2 mmHg, m.p. 108.5—110°, τ (CDCl₃) 1.9br (1H, exch., NH), 3.0 (2H, m, 4- and 5-H), 3.5 (1H, dd, 6-H), 3.8 (1H, s, 3-H), 6.6 (2H, s, exch., NH₂) and 7.8 (3H, s, CH₃) (Found: C, 73.6; H, 6.8; N, 19.4%; M^+ , 146. C₉H₁₀N₂ requires C, 73.9; H, 6.9; N, 19.2%; M , 146).

Reaction of N-Allyl-o-nitroaniline with Acid.—N-Allyl-o-nitroaniline (5.0 g) and concentrated hydrochloric acid (100 ml) were heated under reflux during 48 h. The solution was cooled, basified, and extracted with chloroform. The extract was dried and evaporated *in vacuo*. Chromatography of the residue on alumina gave (a) a mixture (0.7 g), eluted with 5% ethyl acetate in light petroleum, and (b) o-nitroaniline (1.9 g, 26%), eluted with 10% ethyl acetate in light petroleum. The mixture was separated by t.l.c. on silica giving (i) 2-methyl-7-nitroindole (11) (0.16 g, 3%), m.p. 96—97.5°, τ (CDCl₃) 0.2 (1H, s, NH), 1.9 and 2.15 (each 1H, d, 4- and 6-H), 2.8 (1H, d, 5-H), 3.6 (1H, s, 3-H), and 7.5 (3H, s, Me); M^+ 176; (ii) 2-methyl-7-nitro-3-propylindole (12) (0.3 g, 5%), m.p. 90—91°, τ (CCl₄) 0.2 (1H, s, NH), 1.95 and 2.25 (each 1H, d, 4- and 6-H), 2.85 (1H, d, 5-H), 7.5 (3H, s, 2-Me), 7.7 (2H, t, α -CH₂), 8.4 (2H, m, CH₂-CH₂Me), and 9.05 (3H, t, CH₂-CH₃); (iii) 2-methyl-7-nitroindoline (10) (0.01 g, 2%), m.p. 89—91°, τ (CCl₄) 1.6 (1H, s, NH), 1.8 and 2.55 (each 1H, d, 4- and 6-H), 3.15 (1H, d, 5-H), 5.8 (1H, m, 2-H), 6.4 (2H, t, 3-H₂) and 8.35 (3H, d, Me); M^+ 178.

Reactions of o-Phenylenediamines with Dimethyl Acetylenedicarboxylate.—Dimethyl acetylenedicarboxylate (1 equiv.) was added to an ice-cold solution of the amine (2.0 g) in chloroform (20 ml). The solution was allowed to warm to room temperature. After a further 15 min at room temperature, the chloroform was evaporated off and the solid residue was recrystallised.

o-Phenylenediamine gave 3,4-dihydro-3-(methoxycarbonylmethylene)quinoxalin-2(1H)-one (2b) (3.3 g, 82%), m.p. 225° (decomp.) (from light petroleum), ν_{\max} 1740 (ester C=O str) and 1650 (amide C=O str.) cm⁻¹, τ (CF₃·CO₂D) 2.2 (5H, m, ArH and =CH), and 4.1 (3H, s, CO₂Me) (Found: C, 60.4; H, 4.5; N, 12.9%; M^+ , 218. C₁₁H₁₀N₂O₃ requires C, 60.55; H, 4.2; N, 12.8%; M , 218).

N-Allyl-o-phenylenediamine gave 1-allyl-3,4-dihydro-3-(methoxycarbonylmethylene)quinoxalin-2(1H)-one (2c) (2.1 g, 60%), m.p. 109—110° (from light petroleum), ν_{\max} 1670 and 1630 cm⁻¹, τ (CCl₄) —0.9br (1H, exch., NH), 2.9br (4H, ArH), 4.0 (1H, m, CH=CH₂), 4.7 (2H, m, =CH₂), 5.15 (2H, m, NH·CH₂), and 6.25 (3H, s, CO₂Me) (Found: C, 65.0; H, 5.4; N, 10.4%; M^+ , 258. C₁₄H₁₄N₂O₃ requires C, 65.1; H, 5.5; N, 10.85%; M , 258).

N-Propyl-o-phenylenediamine gave 3,4-dihydro-3-(methoxycarbonylmethylene)-1-propylquinoxalin-2(1H)-one (2d) (2.5 g, 72%), m.p. 129—131° (from light petroleum), ν_{\max} 1670 and 1630 cm⁻¹, τ (CDCl₃) —1.1br (1H, exch., NH), 2.6 (4H, m, ArH), 5.7 (2H, t, NH·CH₂), 6.0 (1H, s, =CH), 6.2 (3H, s, CO₂Me), 8.2 (2H, m, CH₂-CH₂Me), and 8.9 (3H, t,

CH₂-CH₃) (Found: C, 64.9; H, 5.9; N, 10.7%; M^+ , 260. C₁₄H₁₆N₂O₃ requires C, 64.6; H, 6.2; N, 10.8%; M , 260).

7-Amino-2-methylindoline gave 1,2,5,6-tetrahydro-2-(methoxycarbonylmethylene)-5-methylpyrrolo[1,2,3-de]quinoxalin-3-one (19) (2.6 g, 75%), m.p. 216—218° (from light petroleum), ν_{\max} 1680 and 1650 cm⁻¹, τ (CDCl₃) —0.9br (1H, exch., NH), 3.05br (3H, ArH), 3.95 (1H, s, =CH), 6.3 (3H, s, CO₂Me), 6.4 (1H, m, 5-H), 7.05 and 7.3 (each 1H, m, 6-H₂), and 8.85 (3H, d, 5-Me) (Found: C, 64.9; H, 5.6; N, 10.95%; M^+ , 258. C₁₄H₁₄N₂O₃ requires C, 65.1; H, 5.5; N, 10.85%; M , 258).

7-Amino-2-methylindole gave 1,2-dihydro-2-(methoxycarbonylmethylene)-5-methylpyrrolo[1,2,3-de]quinoxalin-3-one (14) (2.4 g, 68%), m.p. 163—164° (decomp.) (from toluene), ν_{\max} 1700 and 1650 cm⁻¹; τ (CDCl₃) —1.1br (1H, exch., NH), 2.9 (2H, m, 7- and 8-H), 3.3 (1H, s, 6-H), 3.7 (1H, dd, 9-H), 4.1 (1H, s, =CH), 6.3 (3H, s, CO₂Me), and 7.4 (3H, s, 5-Me) (Found: C, 65.3; H, 4.8; N, 11.0%; M^+ , 256. C₁₄H₁₂N₂O₃ requires C, 65.6; H, 4.7; N, 10.9%; M , 256).

Hydrolysis of Methoxycarbonylmethylenequinoxalines.—The quinoxaline derivative (2.0 g) in 6M-hydrochloric acid (20 ml) was heated under reflux during 1—2 h, cooled, and extracted with chloroform. The extract was dried and evaporated *in vacuo* and the solid residue was recrystallised. In the case of compound (19), the solution was basified before being extracted.

Compound (2b) gave 3-methylquinoxalin-2(1H)-one (6a) (1.1 g, 75%), m.p. 251—252° (lit.^{2,8} 244—245°) (from acetic acid), ν_{\max} 1660 cm⁻¹ (C=O str.); τ [(CD₃)₂SO] —1.98br (1H, exch., NH), 2.2 (1H, dd, 5-H), 2.6 (3H, m, 6-, 7-, and 8-H), and 7.4 (3H, s, Me) (Found: C, 67.2; H, 5.15; N, 17.5%; M^+ , 160. Calc. for C₉H₈N₂O: C, 67.5; H, 5.0; N, 17.5%; M , 160).

Compound (2c) gave 1-allyl-3-methylquinoxalin-2(1H)-one (6b) (1.25 g, 86%), m.p. 56—57° (from light petroleum), ν_{\max} 1660 (C=O str.); τ (CCl₄) 2.25 (1H, dd, 5-H), 2.6 (3H, m, 6-, 7-, and 8-H), 4.0 (1H, m, CH₂-CH=), 4.8 (2H, m, =CH₂), 5.25 (2H, m, NH·CH₂), and 7.55 (3H, s, Me) (Found: C, 72.0; H, 6.0; N, 14.1%; M^+ , 200. C₁₂H₁₂N₂O requires C, 72.0; H, 6.0; N, 14.0%; M , 200).

Compound (2d) gave 3-methyl-1-propylquinoxalin-2(1H)-one (6c) (1.1 g, 71%), m.p. 47—49° (from light petroleum), ν_{\max} 1660 cm⁻¹ (C=O str.); τ (CCl₄) 2.25 (1H, dd, 5-H), 2.6 (3H, m, 6-, 7-, and 8-H), 5.95 (2H, t, NH·CH₂), 7.55 (3H, t, 3-Me), 8.25 (2H, m, CH₂-CH₃), and 9.0 (3H, t, CH₂-CH₃) (Found: C, 70.8; H, 6.9; N, 14.2%; M^+ , 202. C₁₂H₁₄N₂O requires C, 71.3; H, 7.0; N, 13.85%; M , 202).

Compound (19) gave 1,2,5,6-tetrahydro-5-methyl-2-methyl-enepyrrolo[1,2,3-de]quinoxalin-3-one (17) (0.85 g, 58%), m.p. 171—173° (from toluene), ν_{\max} 3180 (N-H str.), and 1680 (C=O str.) cm⁻¹; τ (CDCl₃) 0.1br (1H, exch., NH), 3.2 (3H, s, ArH), 4.9 and 5.8 (each 1H, s, =CH₂), 5.5 (1H, m, 5-H), 7.05 and 7.35 (each 1H, m, 6-H₂), and 8.6 (3H, d, Me) (Found: C, 71.6; H, 6.1; N, 14.2%; M^+ , 200. C₁₂H₁₂N₂O requires C, 72.0; H, 6.0; N, 14.0%; M , 200).

Compound (14) gave 2,5-dimethylpyrrolo[1,2,3-de]quinoxalin-3-one (15) (0.65 g, 44%), m.p. 151—152° (from toluene), ν_{\max} 1660 cm⁻¹ (C=O str.); τ (CCl₄) 2.7 (3H, m, ArH), 3.8 (1H, s, 6-H), 7.4 (3H, s, Me), and 7.6 (3H, s, Me) (Found: C, 72.5; H, 5.1; N, 14.2%; M^+ , 198. C₁₂H₁₀N₂O requires C, 72.7; H, 5.1; N, 14.3%; M , 198).

We thank the S.R.C. for a C.A.P.S. Award (to R. A. W.) and Dr. H. F. Ridley, Ciba-Geigy (U.K.) Ltd., for his interest and for discussion.

⁸ O. Hinsberg, *Annalen*, 1896, **292**, 245.