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A NEW SYNTHESIS OF 3H-PHENOXAZIN-3-ONES

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Abstract—The reductive cyclisation of 3-hydroxy-2'-nitrodiphenyl ethers provides a new synthesis of 3H-phenoxazin-3-ones, which should be particularly suitable for the synthesis of actinomycins.

THE 3H-phenoxazin-3-one ring system is a central structural feature of the actinomycin antibiotics (**1**),[1] which find use in cancer chemotherapy. Of the various ring syntheses available only the oxidative coupling of o-aminophenols has proved suitable for actinomycin preparation. One disadvantage of this approach is that the coupling of pairs of aminophenols with different peptide side chains results in difficult separable mixtures of all four possible products, and the relative positions of the peptide side-chains are not readily ascertained. Further, analogues having substituents at positions 7 and 8 are not accessible, although substituents may be introduced into preformed actinomycins at position 7 by a circuitous route. It occurred to us that a more flexible synthetic route might be devised based upon the cyclisation of appropriate 3-hydroxy-2'-nitrodiphenyl ethers. The present paper describes the realisation of this idea.

The necessary ethers (**2–9**) were not reported in the literature, but they were readily obtained by reaction of appropriate o-chloronitrobenzenes with potassium m-hydroxyphenoxides. In accord with observations in the literature[2] attempts to prepare these compounds from o-nitrophenols and m-iodoanisole were unsuccessful. Alternatively, reaction of the o-chloronitrobenzene with m-methoxyphenol yielded the corresponding methyl ethers **10**, **11**, which were cleaved conveniently to the corresponding phenols **2**, **3** with boron trichloride. In the case of **10** treatment with boron tribromide led to cleavage of the aryl-oxygen bond with formation of o-bromonitrobenzene and m-methoxyphenol.

Among other reagents examined for the cleavage of **10–2** was aluminium chloride. Although only a modest yield of **2** was obtained an interesting feature was the production of small amounts of two phenoxazinones. One was readily identified as 3H-phenoxazin-3-one and the other, on the basis of analytical and spectroscopic data, as a methoxy derivative. Consideration of possible modes of formation suggested it was the previously unknown 1-methoxy-3H-phenoxazin-3-one. An analogy for these cyclisations is provided by the aluminium chloride mediated reaction of o-nitrobenzyl chloride with benzene to form o-nitrodiphenylmethane and acridine N-oxide.[3] A sample of the previously undescribed 3H-phenoxazin-3-one N-oxide was prepared by oxidation of **12** with m-chloroperbenzoic acid, but none of this compound could be detected in the complex mixture resulting from treatment of **10** with aluminium chloride.

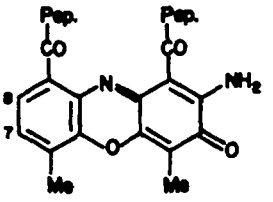
The results with aluminium chloride encouraged an extensive investigation of the acid catalysed cyclisation of the ether (**2**), especially as several comparable cyclisations have been recorded in the literature.[4] However, conditions leading to preparatively useful cyclisations could not be established. The best yield, *ca* 5% of 3H-phenoxazin-3-one (**12**), was achieved when the ether was heated with 6% sulphuric acid in acetic acid. None of the anticipated N-oxide could be detected in the mixture but small amounts of 7-hydroxy-3H-phenoxazin-3-one (**20**) were isolated. Suspicions that the latter compound resulted from rearrangement of the N-oxide were dispelled when it was found that 3H-phenoxazin-3-one (**12**) gave a good yield of its 7-hydroxy-derivative under the reaction conditions. Only slightly better yields of 7-methylphenoxazone (**13**) were obtained when the ether (**3**) was similarly treated, even though oxidation at C7 was precluded.

A satisfactory cyclisation procedure was eventually devised based upon the base-catalysed condensation of aromatic nitroso compounds with phenols to form indophenols. Reduction of the ether **2** with Zn dust and ammonium chloride in aqueous 1,2-dimethoxyethane gave a colourless solution. Aeration of this solution, after filtering off the excess Zn, provided a 67% yield of 3H-phenoxazin-3-one (**12**). Comparable yields were obtained for the conversion of the ethers **3** to **6** into the corresponding 3H-phenoxazin-3-ones **13–16**. A reasonable yield was even obtained of the rather unstable 2-hydroxy-3H-phenoxazin-3-one, although in this case the methylenedioxy group of the precursor was cleaved with boron trichloride and the crude product cyclised directly.

The cyclisation of the ethers (**7–9**) only proceeded as far as the respective 3-hydroxyphenoxazines (**21–23**) as the 1-carbomethoxy group raised the redox potential of these compounds above that of oxygen in the weakly basic medium. However, these dihydro compounds could be satisfactorily converted to the corresponding phenoxazones (**17–19**) by brief oxidation with ferric chloride in acetic acid.

The reduction conditions employed in this cyclisation procedure are those normally proscribed for converting aromatic nitro-compounds to arylhydroxylamines. However, cyclisation of the species D (of Scheme 1) to the hydroxyphenoxazine E appears most unlikely under tha present conditions since closely analogous processes only occur[5] in strongly acidic media. An alternative route in which D is converted by the aerial oxidation step into the nitroso compound B followed by intramolecular cyclisation can also be dismissed as the products should always be phenoxazinones (C), whereas **7–9** yielded only the hydroxyphenoxazines. Thus, we conclude that the reaction follows the pathway originally anticipated namely A→B→C→E, with the aeration step serving merely to reconvert E–C.

Following ample precedence[6] the initial scheme for



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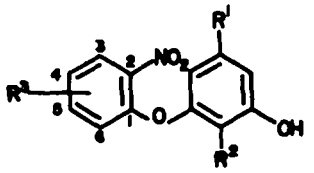
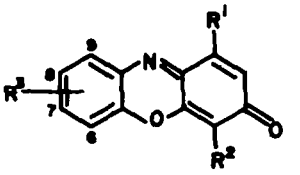
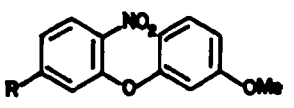


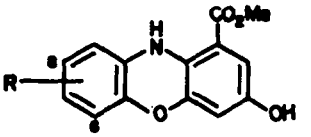
2 $R^1 = R^2 = R^3 = H$
3 $R^1 = R^2 = H$, $R^3 = 5\text{-Me}$
4 $R^1 = R^2 = H$, $R^3 = 4\text{-Cl}$
5 $R^1 = Me$, $R^2 = R^3 = H$
6 $R^1 = R^3 = H$, $R^2 = Me$
7 $R^1 = CO_2Me$, $R^2 = R^3 = H$
8 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = 4\text{-}CO_2Me$
9 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = 6\text{-}CO_2Me$



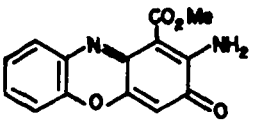
12 $R^1 = R^2 = R^3 = H$
13 $R^1 = R^2 = H$, $R^3 = 7\text{-Me}$
14 $R^1 = R^2 = H$, $R^3 = 8\text{-Cl}$
15 $R^1 = Me$, $R^2 = R^3 = H$
16 $R^1 = R^3 = H$, $R^2 = Me$
17 $R^1 = CO_2Me$, $R^2 = R^3 = H$
18 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = 8\text{-}CO_2Me$
19 $R^1 = CO_2Me$, $R^2 = H$, $R^3 = 6\text{-}CO_2Me$
20 $R^1 = R^2 = H$, $R^3 = 7\text{-OH}$



10 R = H
11 R = Me



21 R = H
22 R = 8-CO_2Me
23 R = 6-CO_2Me



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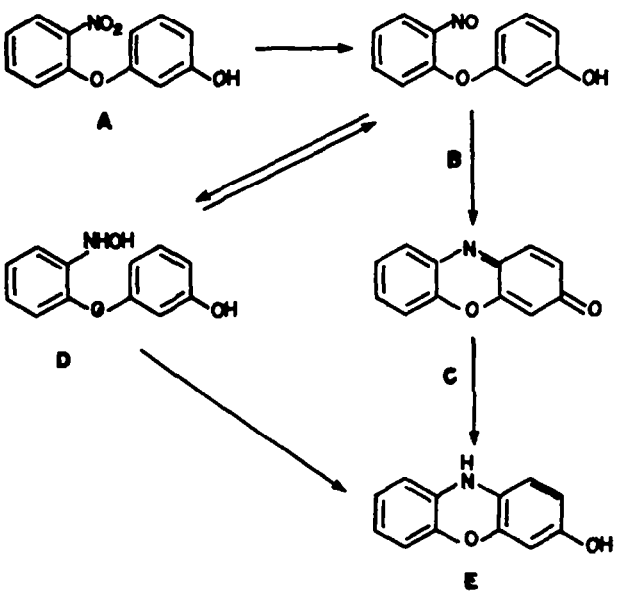

A B C D E

Scheme 1.

actinomycin synthesis envisaged the introduction of the 2-amino group by nucleophilic substitution of the preformed phenoxazone. However, it has proved possible to proceed directly from 7 to 24 in 60% overall yield by increasing both the initial ammonium chloride concentration and the subsequent aeration temperature. Presumably the increased temperature facilitates the aerial oxidation of 21–17, which then undergoes addition of ammonia and re-oxidation.

EXPERIMENTAL

NMR spectra were measured at 60 MHz on a Perkin-Elmer R12B spectrometer for $CDCl_3$ solns with internal TMS unless otherwise stated. IR spectra were recorded for Nujol or hexachlorobutadiene mulls on a Unicam SP 200 spectrophotometer and UV spectra for EtOH solns on a Unicam SP 800 instrument. Mass spectra were recorded by the U. of L. Mass Spectrometry Service at Q.E.C. on an MS 30.

Preparation of 3'-hydroxy-2-nitrodiphenyl ethers

Method A. Resorcinol (11 g) was added to an ethanolic soln (100 ml) of KOEt (from 3.9 g of metal) and the soln evaporated to dryness. o-Nitrochlorobenzene (15.8 g) was added and the mixture heated gradually to 110° and then kept at this temp. for 1½ hr. The mixture was cooled, dissolved in 10% NaOH (400 ml) and non-phenolic products extracted with ether. The alkaline soln was acidified with 4N HCl and extracted with ether. The ether extract was washed with water, dried (Na_2SO_4) and evaporated. The crude product was chromatographed on silica gel in benzene to give 3-hydroxy-2'-nitrodiphenyl ether (25%) m.p. 39–40° from benzene-petroleum ether (40–60°). (Found: C, 62.6; H, 4.1; N, 5.9. Calc. for $C_{12}H_9NO_4$: C, 62.3; H, 3.9; N, 6.1%); IR 3460, 1540, 1360 cm^{-1}; MS *m/e* 231 (85), 214 (8), 198 (15), 186 (10), 185 (13), 184 (11), 172 (5), 170 (4), 158 (12), 157 (9), 128 (22), 122 (100).

A modified procedure in which the above reactants were heated at 110–120° for 2 hr with cuprous oxide (14.3 g) in N,N-dimethylformamide (200 ml) gave a 31% yield. Following the initial procedure:

(i) 5-Methyl-2-nitrochlorobenzene and resorcinol gave 3'-hydroxy-5-methyl-2-nitrodiphenyl ether (30%) m.p. 108–109° from benzene (Found: C, 63.8; H, 4.4; N, 5.5. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7%); IR 3450, 1510, 1350 cm^{-1}; NMR δ 2.32 (s, CH_3), 5.8 (br.s., OH), 6.5–8.1 (m, 7H, ArH).

(ii) 2,5-Dichloronitrobenzene and resorcinol gave 4-chloro-3'-hydroxy-2-nitrodiphenyl ether (23%) as a viscous liquid (Found: N, 5.6. Calc. for $C_{12}H_8ClNO_4$; N, 5.3%). IR 3400, 1540, 1360 cm^{-1}; MS *m/e* 267 (10), 265 (30), 229 (50), 217 (10), 174 (50), 149 (35), 147 (50), 143 (25), 131 (75), 129 (25), 123 (20), 119 (25), 117 (100), 111 (25), 105 (60), 104 (55), 103 (45), 100 (50), 79 (75).

(iii) 5-Methylresorcinol and o-chloronitrobenzene gave 3-hydroxy-5-methyl-2'-nitrodiphenyl ether (38%) m.p. 89–90° from benzene (Found: C, 63.9; H, 4.5; N, 5.7. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7%); IR 3475, 1530, 1360 cm^{-1}; NMR δ 2.1 (s, CH_3), 5.35 (br, OH), 6.5–8.2 (m, 7H, ArH).

(iv) 2-Methylresorcinol and o-chloronitrobenzene gave 3-hydroxy-2-methyl-2'-nitrodiphenyl ether (23%) m.p. 89–91° from benzene. (Found: C, 63.7; H, 4.5; N, 5.3. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7%); IR 3500, 1520, 1346 cm^{-1}; NMR δ 2.1 (s, CH_3); 5.3 (br, OH), 6.4–8.3 (m, 7H, ArH).

Method B. Methyl 3,5-dihydroxybenzoate was added to a methanolic (100 ml) soln of KOMe (from 2 g of metal), and the soln evaporated to dryness. The residue was mixed with o-chloronitrobenzene (7.8 g) and cuprous oxide (7.2 g) in N-methylpyrrolidone (100 ml) and heated at 150–160° for 2 hr. To the cooled mixture was added 4N HCl (200 ml) and water (400 ml). The products were collected by ether extraction and chromatographed on silica gel in benzene. Elution with benzene-EtOAc gave 3-carbomethoxy-5-hydroxy-2'-nitrodiphenyl ether (8.9 g, 62%) m.p. 113–115° from aq. alcohol (Found: C, 58.4; H, 3.9; N, 4.9. Calc. for $C_{14}H_{11}NO_4$: C, 58.1; H, 3.8; N, 4.8%); IR 3300, 1690, 1535, 1340 cm^{-1}; NMR δ 3.78 (s, CH_3); 6.7–8.2 (m, 7H, ArH); MS *m/e* 289 (25), 258 (8), 228 (6), 211 (10), 200 (4), 199 (6), 184 (45), 171 (5), 155 (25), 128 (40), 127 (30), 122 (100).

This product was preceded by methyl 3,5-bis(o-nitrophenoxy) benzoate (1.5 g, 15%) m.p. 154–6° from n-hexanol. (Found: C, 58.5; H, 3.5; N. 6.8. Calc. for $C_{26}H_{14}N_2O_8$: C, 58.5; H, 3.4; N, 6.8%); IR 1710, 1525, 1342 cm^{-1}; NMR δ 3.86 (s, CH_3), 6.9–8.3 (m, 11H, ArH); MS *m/e* 410 (24), 332 (10), 288 (3), 272 (6), 258 (3), 202 (2), 183 (6), 182 (4), 155 (10), 139 (8), 122 (100).

Following this procedure:-

(i) Methyl 4-chloro-3-nitrobenzoate and methyl 3,5-dihydroxybenzoate gave 3,4'-dicarbomethoxy-5-hydroxy-2'-nitrodiphenyl ether (62%) m.p. 131–132° from benzene. (Found: C, 54.9, H, 3.7; N, 4.0. Calc. for $C_{16}H_{13}NO_8$: C, 55.3; H, 3.8; N, 4.0%); IR 3200, 1710, 1685, 1535, 1342 cm^{-1}; NMR δ 3.85 (s, CH_3), 3.93 (s, CH_3), 6.8–8.7 (m, 6H, ArH); MS *m/e* 347 (35), 316 (10), 315 (20), 286 (3), 269 (6), 257 (10), 242 (5), 211 (10), 198 (5), 197 (8), 180 (100), 149 (10), 143 (12), 119 (15). Additionally there was formed a small amount (13%) of methyl 3,5-bis(4'-carbomethoxy-2'-nitrophenoxy) benzoate m.p. 156° from n-hexanol. (Found: C, 54.7; H, 3.5; N, 5.3. Calc. for $C_{24}H_{18}N_2O_{12}$: C, 54.8; H, 3.4; N, 5.3:); IR 1710, 1535, 1340 cm^{-1}; NMR δ 3.93 (s, CH_3), 4.0 (s, $2\times CH_3$), 7.1–8.8 (m, 9H, ArH); MS *m/e* 526 (10), 361 (50), 332 (35), 331 (15), 300 (4), 278 (8), 271 (10), 256 (8), 212 (55), 197 (15), 175 (20), 161 (35), 120 (15), 83 (100).

(ii) Methyl 2-chloro-3-nitrobenzoate and methyl 3,5-dihydroxybenzoate gave 2'-3-dicarbomethoxy-5-hydroxy-6'-nitrodiphenyl ether (52%) m.p. 167–169° from benzene (Found: C, 55.0; H, 3.7; N, 4.1. Calc. for $C_{16}H_{13}NO_8$: C, 55.3; H, 3.7; N, 4.0%); IR 3400, 1700, 1538, 1350 cm^{-1}; NMR δ 3.65 (s, CH_3), 3.78 (s, CH_3); 6.5–8.5 (m, 6H, ArH); MS *m/e* 347 (10), 285 (10), 149 (6), 119 (8), 113 (12), 93 (12), 79 (24), 78 (20), 69 (100).

Method C. o-Nitrochlorobenzene (15.8 g) was heated at 140–150° for 3 hr with potassium m-methoxyphenoxide prepared by evaporation of a solution of m-methoxyphenol (12.4 g) in ethanolic KOEt from K metal (3.9 g). The cooled mixture was extracted with ether and the soln washed with dil NaOH. The ethereal soln was dried (Na_2SO_4) and evaporated. The crude product was crystallised from cyclohexane to give 3-methoxy-2'-nitrodiphenyl ether (18.5 g, 75%) m.p. 53.–54°. (Found: C, 63.9; H, 4.2; N, 5.6. Calc. for $C_{13}H_{11}NO_4$: C, 63.7; H, 4.5; N, 5.7%); IR 1535, 1355 cm^{-1}; NMR δ 3.72 (s, CH_3), 6.5–8.1 (m, 8H, ArH).

Boron trichloride (1 ml) was added dropwise to a stirred soln of the ether (10) (1.2 g) in CH_2Cl_2 at −80° over a period of ½ hr. The temp was then allowed to rise slowly and the mixture was eventually refluxed for 7 hr. The mixture was evaporated *in vacuo* and the residue extracted with dil NaOH and ether. The aqueous extract was acidified and ether extracted. The dried (Na_2SO_4) ether extract was evaporated and the residue chromatographed on silica gel in benzene to give 3-hydroxy-2'-nitrodiphenyl ether (0.75 g, 66%).

Following this procedure:

(i) 3-Chloro-4-nitrotoluene and m-methoxyphenol gave 3'-methoxy-5-methyl-2-nitrodiphenyl ether (67%) b.p. 168° 0.02 mm. (Found: C, 64.3; H, 5.0; N, 5.6. Calc. for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.0; N, 5.4%); IR 1530, 1355 cm^{-1}; NMR δ 2.31 (s, CH_3), 3.79 (s, CH_3). 6.5–8.1 (m, 7H, ArH). Cleavage with boron trichloride gave 3'-hydroxy-5-methyl-2-nitrodiphenyl ether (75%).

(ii) 3,4-Methylenedioxyphenol and o-nitrochlorobenzene gave 3,4-methylenedeoxy-2'-nitrodiphenyl ether (79%) m.p. 83–85° from benzene-cyclohexane (1:9). (Found: C, 60.1; H, 3.5; N, 5.4. Calc. for $C_{13}H_9NO_5$: C, 60.2; H, 3.5; N, 5.4%); IR 1525, 1345 cm^{-1}; NMR δ 6.1 (s, CH_2), 6.5–8.1 (m, 7H, ArH). The crude product resulting from boron trichloride treatment was used directly for reductive cyclisation to 2-hydroxy-3H-phenoxazin-3-one.

Reaction of 3-methoxy-2'-nitrodiphenyl ethers with aluminium chloride

A stirred soln of 3-methoxy-2'-nitrodiphenyl ether (5 g) and anhydrous $AlCl_3$ (5 g) in dry chlorobenzene (100 ml) was heated under reflux for 2 hr. The cooled mixture was poured into ice-cold 15% HCl (200 ml) and ether extracted. The dried (Na_2SO_4) ethereal extract was evaporated *in vacuo*. Three compounds were separated from the residue by column chromatography and subsequent prep. tlc in benzene-EtOAc (9:1):- (a) 3-hydroxy-2'-nitrodiphenyl ether (0.7 g); (b) 3H-phenoxazin-3-one (0.23 g) m.p.

215-7° (lit[7] m.p. 216-7°); UV 449 (10,934), 350 (13,650) nm; IR 1650, 1622 cm^{-1}; MS *m/e* 197 (100), 169 (70), 143 (5), 141 (4), 140 (10), 115 (9), 114 (10); identical with an authentic sample; (c) 1(?)-methoxy-3H-phenoxazin-3-one (0.18 g) m.p. 135–140 (dec.). (Found: C, 69.3; H, 4.1; N, 6.2. Calc. for $C_{13}H_9NO_3$: C, 68.7; H, 4.0; N, 6.2%); UV 465, 325 nm.

Similar treatment of 3'-methoxy-5-methyl-2-nitrodiphenyl ether gave (a) 3'-hydroxy-5-methyl-2-nitrodiphenyl ether (15%); (b) 7-methyl-3H-phenoxazin-3-one (6%) m.p. 189–90° from EtOH (Found: C, 74.0; H, 4.3; N, 6.7. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); UV 452 (11820), 366 (11290) nm; IR 1645, 1620 cm^{-1}; NMR δ 2.48 (s, CH_3), 6.2–7.9 (m, 6H, ArH); MS *m/e* 211 (100), 183 (70), 149 (10), 146 (5), 128 (5), 83 (20); (c) *x*-hydroxy-7-methyl-3H-phenoxazin-3-one (4%) m.p. 180–182° from EtOH; UV 465 nm in neutral or acid soln., 480 nm in basic soln; IR 3350, 1655, 1620 cm^{-1}; MS *m/e* 227 (100), 213 (15) 199 (50), 184 (10), 167 (6), 156 (4); room temp reduction of a 60% aq. EtOH soln with ammonium chloride and Zn dust gave a colourless soln which regenerated the phenoxazone on filtration and aeration; (d) x-(chlorophenyl)-7-methyl-3H-phenoxazin-3-one (2%) m.p. 139–140° from benzene; UV 465, 362, 256 nm; IR 1655, 1620; MS *m/e* 323 (33), 321 (100); 293 (15); 286 (22), 258 (6), 215 (8).

3H-Phenoxazin-3-one N-oxide

A soln of phenoxazinone (0.2 g) and m-choroperbenzoic acid (0.4 g) in $CHCl_3$ (40 ml) was stirred at room temp in the dark for 24 hr. After washing with dil Na_2CO_3 and drying (Na_2SO_4) the $CHCl_3$ was evaporated *in vacuo*. The residue was chromatographed on silica gel in benzene-EtOAc (9:1) to separate a little unreacted 3H-phenoxazin-3-one from the N-oxide (0.1 g, 47%) m.p. 162–5° from benzene. UV 486 (14,700), 368 (16,400), nm; IR 1723, 1626 cm^{-1}; MS *m/e* 213 (10), 197 (100), 185 (9), 169 (65), 167 (48), 140 (15), 113 (30): A small sample in 60% aq. ethanol was reduced by stirring for 10 min with Zn dust and ammonium chloride. Aeration of the filtered colourless soln gave an orange coloured product with the same TLC R_f value as 3H-phenoxazin-3-one.

Acid catalysed cyclisation of 3-hydroxy-2'-nitrodiphenyl ethers

A soln of 3-hydroxy-2'-nitrodiphenyl ether (1 g) in AcOH (15 ml) containing H_2SO_4 (1 ml) was refluxed for 2 hr. The mixture was diluted with water and neutralised with Na_2CO_3. The products were extracted with ether and separated by preparative TLC using benzene–EtOAc (9:1). The principal components identified were 3H-phenoxazin-3-one (5%), and 7-hydroxy-3H-phenoxazin-3-one (5%) identified by spectroscopic and chromatographic comparison with an authentic sample. UV 476 nm (neutral), 574 nm (basic); MS *m/e* 213 (100), 185 (50), 170 (60), 169 (15), 153 (45), 149 (30), 131 (36), 130 (15), 122 (15), 119 (30), 115 (60), 109 (90).

Treatment of 3H-phenoxazin-3-one under the same conditions led to the isolation of 7-hydroxy-3H-phenoxazin-3-one (60%).

A complex mixture of products was similarly obtained from 3'-hydroxy-5-methyl-2-nitrodiphenyl ether and careful separation provided 7-methyl-3H-phenoxazin-3-one (6%).

Reductive cyclisation of 3-hydroxy-2'-nitrodiphenyl ethers

3-Hydroxy-2'-nitrodiphenyl ether (1 g) and ammonium chloride (0.5 g) were dissolved in 60% aqueous 1,2-dimethoxyethane (25 ml.). Zinc dust (1.25 g) was added in small portions to the stirred soln over a period of 20 min and the mixture stirred for a further 30 min at 30–40°. It was then filtered and the residue washed with hot 1,2-dimethoxyethane. The combined filtrates were stirred at room temp with free access of air for *ca* 7 hr, diluted with water and extracted with ether. Evaporation of the ether extract and crystallisation of the residue from aqueous alcohol provided 3H-phenoxazin-3-one (0.57 g, 67%).

Following this procedure:

(i) 3'-Hydroxy-5-methyl-2-nitrodiphenyl ether gave 7-methyl-3H-phenoxazin-3-one (63%):

(ii) 4-Chloro-3'-hydroxy-2-nitrodiphenyl ether yielded 8-chloro-3H-phenoxazin-3-one (56%) m.p. 227–30° from benzene (Found: C, 61.9; H, 2.6; N, 6.0. Calc. for $C_{12}H_6ClNO_2$: C, 62.2; H, 2.6; N, 6.0%); UV 457 (12,230), 340 (14,800) nm; IR 1650, 1630 cm^{-1}; MS *m/e* 233 (20), 231 (80), 205 (22), 203 (100), 140 (30).

(iii) 3-Hydroxy-5-methyl-2'-nitrodiphenyl ether provided 1-methyl-3H-phenoxazin-3-one (67%) m.p. 198–9° from aq. EtOH (lit. m.p. 198–9°). (Found: C, 73.9; H, 4.4; N, 6.7. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); UV 447 (11,390), 350 (15,825) nm; IR 1658, 1620 cm^{-1}; NMR δ 2.4 (s, CH_3), 6.2–8.0 (m, 6H, ArH); MS *m/e* 211 (95), 183 (100); 182 (40); 155 (10), 154 (55), 127 (5).

(iv) 3-Hydroxy-2-methyl-2'-nitrodiphenyl ether gave 4-methyl-3H-phenoxazin-3-one (73%) m.p. 163–5° from aq. EtOH. (Found: C, 74.0; H, 4.3; N, 6.7. Calc. for $C_{13}H_9NO_2$: C, 73.9; H, 4.3; N, 6.6%); UV 460 (8340), 345 (12340) nm; IR 1650, 1614 cm^{-1}; NMR δ 2.1 (s, CH_3), 6.6–8.0 (m, 6H, ArH); MS *m/e* 211 (100), 184 (4), 183 (30), 182 (28), 155 (12), 154 (50), 129 (5), 128 (9), 127 (7).

(v) 3,4-Dihydroxy-2'-nitrodiphenyl ether, as obtained direct from the methylene ether, provided 2-hydroxy-3H-phenoxazin-3-one (31%) dec > 240° from EtOH (lit[8] m.p. 264° dec) identical to an authentic sample in respect of TLC and spectroscopic properties. UV 400 (13,870) nm shifted to 414 nm with shoulder at 436 nm in alkali; IR 3250, 1650, 1610 cm^{-1}; MS *m/e* 213 (100), 185 (90), 170 (30), 156 (10), 144 (12), 137 (10), 129 (15), 122 (20), 109 (30).

(vi) 3-Carbomethoxy-5-hydroxy-2'-nitrodiphenyl ether yielded 1-carbomethoxy-3-hydroxyphenoxazine (80%) m.p. 191–2° from aq. EtOH. (Found: C, 65.7; H, 4.4 N, 5.2. Calc. for $C_{14}H_{11}NO_4$: C, 65.4; H, 4.3; N, 5.5%); IR 3500, 3375, 1680 cm^{-1}; NMR δ 3.88 (s, CH_3), 6.4–7.0 (m, 6H, ArH), 8.5–8.8 (br, 1H, exchangeable, OH/NH); MS *m/e* 257 (70), 256 (5), 255 (10), 225 (30), 198 (20), 197 (100), 196 (15), 169 (10), 140 (8), 113 (20). The phenoxazine (0.5 g) was dissolved in AcOH and mixed with a concentrated aqueous soln of $FeCl_3$ (4.5 g). The initial blue colour changed rapidly to orange-red. After 5 min stirring, the mixture was diluted with water and $CHCl_3$ extracted. The crude product thus obtained was purified by chromatography on silica gel and eluting with benzene-EtOAc (7:3). Recrystallisation from benzene gave 1-carbomethoxy-3H-phenoxazin-3-one (0.37 g, 75%) m.p. 193–195°. (Found: C, 65.7; H, 3.6; N, 5.4. Calc. for $C_{14}H_9NO_4$: C, 65.9; H, 3.5; N, 5.5%); UV 459 (10,200), 355 (10,330) nm; IR 1735, 1615 cm^{-1}; NMR δ 3.98 (s, CH_3), 6.3–8.0 (m, 6H, ArH); MS *m/e* 255 (45), 204 (5), 196 (100), 169 (13), 140 (15), 113 (15).

(vii) 3,4'-Dicarbomethoxy-5-hydroxy-2'-nitrodiphenyl ether gave 1,8-dicarbomethoxy-3-hydroxyphenoxazine (90%) from n-hexanol partially melting 280–285° becoming orange-red, then decolourising and decomposing > 308°. (Found: C, 60.6; H, 4.1; N, 4.3. Calc. for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.1; N, 4.4%); IR. 3400, 3300, 1685, 1635 cm^{-1}; NMR δ 3.75 (s, CH_3), 3.79 (s, CH_3), 6.4–8.6 (m, 5H, ArH); MS *m/e* 315 (2), 229 (100), 214 (7), 213 (6), 212 (7), 196 (5), 186 (4), 138 (5), 123 (25), 122 (10), 108 (10), 93 (20). Oxidation provided 1,8-dicarbomethoxy-3H-phenoxazin-3-one (70%) m.p. 174–6° from benzene. (Found: C, 60.8; H, 3.6; N, 4.4. Calc. for $C_{16}H_{11}NO_6$: C, 61.3; H, 3.5; N, 4.5%); UV 430 (13,770), 330 (9,700) nm; IR 1730, 1720, 1640, 1620 cm^{-1}; NMR δ 4.15 (s, $2\times CH_3$), 6.4–8.5 (m, 5H, ArH); MS *m/e* 313 (60), 282 (30), 255 (100), 254 (70), 227 (4), 196 (6), 126 (5), 112 (6).

(viii) 2',3-Dicarbomethoxy-5-hydroxy-6'-nitrodiphenyl ether provided 1,6-dicarbomethoxy-3-hydroxyphenoxazine (93%) m.p. 258–61° from n-hexanol. (Found: C, 60.6; H, 4.1; N, 4.5. Calc. for $C_{16}H_{13}NO_6$: C, 60.95; H, 4.1; N, 4.4%); IR 3430, 3355, 1710, 1690, 1640 cm^{-1}; NMR δ 3.3 (br, NH), 3.8 (s, $2\times CH_3$), 6.3–7.2 (m, 5H, ArH), 8.6 (br, OH); MS *m/e* 315 (60), 283 (20), 255 (100), 224 (3), 198 (5), 196 (10), 169 (4), 140 (12). Oxidation yielded 1,6-dicarbomethoxy-3H-phenoxazin-3-one (77%) m.p. 187–9° from benzene. (Found: C, 61.3; H, 3.6; N, 4.3. Calc. for $C_{16}H_{11}NO_6$: C, 61.3, H, 3.5; N, 4.5%); UV 456 (10,200), 340 (13,700) nm; IR 1720, 1635 cm^{-1}; NMR δ 4.02 (s, $2\times CH_3$); 6.5–8.4 (m, 5H, ArH); MS *m/e* 313 (100), 282 (30), 256 (10), 227 (5), 196 (5), 195 (5), 140 (5), 126 (10), 112 (15).

Preparation of 2-amino-1-carbomethoxy-3H-phenoxazin-3-one

5-Carbomethoxy-3-hydroxy-2'-nitrodiphenyl ether (1 g) and ammonium chloride (1 g) were dissolved in 60% aq 1,2-dimethoxyethane (30 ml). Zinc dust (1.5 g) was added in small lots to the stirred soln over 15 min and the temp kept below 40°.

Subsequently the mixture was stirred for a further 20 min at 40–45°. It was then filtered and the residue washed with hot aq 60% 1,2-dimethoxyethane (30 ml). The combined filtrate and washings were stirred with access of air at 60–70° for 4 hr when an orange-red solid separated from the initially colourless soln. The cooled soln was diluted with water (400 ml) and extracted with EtOAc. The extract was dried (Na_2SO_4) and evaporated *in vacuo*. The major component of the residue was separated from minor amounts of 1-carbomethoxy-3-hydroxyphenoxazine (125 mg) and 2'-amino-5-carbomethoxy-3-hydroxydiphenyl ether (75 mg) by eluting with benzene-EtOAc (7:3) through a small chromatographic column of silica gel. 2-Amino-1-carbomethoxy-3H-phenoxazin-3-one was obtained from MeOH as orange-red needles (0.56 g, 60%), m.p. 221–223° (Found: C, 62.4; H, 3.5; N, 10.3. Calc. for $C_{14}H_{10}N_2O_4$: C, 62.2; H, 3.7; N, 10.3%); UV 432 (12,000) nm in neutral soln shifting to 457 nm with shoulders at 424 and 494 nm in strong acid; IR 3405, 3300, 1660, 1578, 1340, 1250, 850, 760, 735 cm^{-1}; NMR (C_5D_5N) δ 3.9 (s, 3H, CH_3), 6.53 (br, 2H, NH_2); MS *m/e* 270 (81), 239 (5), 238 (13), 211 (74), 210 (100), 183 (6), 182 (6), 156 (11), 155 (10), 128 (13).

2'-Amino-5-carbomethoxy-3-hydroxydiphenyl ether became the major product (65%) when the reduction temp was 50–60°, m.p. 181–184° from benzene-EtOH (Found: C, 65.2; H, 5.2; N, 5.4. Calc. for $C_{14}H_{13}NO_4$: C, 64.9; H, 5.0; N, 5.4%); IR 3310, 3250, 1510 cm^{-1}; NMR δ 2.7–3.3 (br, 2H, NH_2), 4.3–4.8 (br, 1H, OH), 6.5–7.3 (m, 7H, ArH); MS *m/e* 259 (15), 228 (4), 199 (22), 170 (6), 160 (4), 120 (5), 109 (10), 108 (30), 92 (20), 80 (100).

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