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SYNTHESIS OF AZAPHENOXAZIN AND PHENOTHIAZIN–3–ONES

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The cyclisation of 3–hydroxy–2′–nitrodiphenyl ethers provided a novel and convenient route to 3H–phenoxazin–3–ones. This paper describes further exploitation of the procedure to the synthesis of other hetrocycles. Thus preparation of azaphenoxazin and phenothiazin–3–ones was attempted from 2–(3′–hydroxyphenoxy)–3–nitropyridines and 3–hydroxy–2′–nitrodiphenyl sulphides.

INTRODUCTION

Azaphenoxazinones (5; Z=N,X=O) and phenothiazinones (5; Z=C,X=S) are known for their pharmacological activities [1, 2]. Thus azaphenoxazones have been used as pesticides, bactericides, herbicides, analgesic and CNS depressant etc. Similarly, phenothiazines, apart from their applicability as insecticides and fungicides, are widely used in pharmaceuticals. They act as anthelminic, urinary antiseptic, antihistaminic, antiemitic, antivertigo agent and in treating worm infections. In addition, several phenothiazinimum salts are used as dyestuffs. For example, methylene blue is used as biological stain, redox indicator and in dyeing cotton. Such important usefulness of these heterocycles prompted their synthesis from different routes but the methods thus far developed are resticted in their applicability. Thus the accessibility of the starting materials, ease of reaction conditions, credibility of the reaction paths as well as overall yield of the final products were the main considerations which envisaged their synthesis from a new route.

MATERIALS AND METHODS

Melting points were taken on a Gallenkamp apparatus and are uncorrected. Microanalyses were performed by the Microanalysis Service, Isotopic Unit, Queen Elizabeth College, London. NMR spectra were recorded at 60 MHz on a Perkin–Elmer R12B spectrometer for $CDCl_3$ solutions with internal TMS. IR spectra were recorded for Nujol mulls on a Unicam SP 200 spectrophotometer and UV spectra for ETOH solutions on a Unicam SP 800 instrument. Mass spectra were recorded on a MS 30 by the U of L Mass Spectrometry Service at Q.E.C. London.

Preparation of 2–(3′–Hydroxy–2′–Methylphenoxy)–3–Nitropyridine (6). 0.025M (4.05 g) monopotassium salt of 2–methyl resorcinol (obtained by mixing equimolar quantities of 2–methyl resorcinol and potassium ethoxide), 0.025M (3.95 g) 2–chloro–3–nitropyridine, cuprous oxide (3.60 g) and 50 ml *N,N*–dimethylformamide were refluxed at 120–40° on an oil bath for two hr. The reaction mixture was then cooled, acidified with 4N HCl (100 ml), diluted with water and, finally, extracted with ethyl acetate (2x75 ml). The combined extracts were dried over anhyd. sodium sulphate and the solvent distilled off. The residue was chromatographed on sillica gel in cyclohexane–chloroform (50:50). The product separated first was identified as 1,3–*bis* (3′–nitro–2′–pyridyloxy)–2–methylbenzene. Shining crystals from ethanol/benzene (10:90). m.p. 197–99°.

Yield: 10.5 g (57%). (Found: C, 55. 19;H, 3.24; N, 15.57. Calc. for $C_{17}H_{12}N_4O_6$: C, 55. 43; H, 3.20; N, 15.22%). IR: 1598, 1520, 1345, 1280, 1240 cm^{-1}. NMR: δ 2.6 (s, 3H, CH_3), 7.07–7.05 and 8.3–8.6 (m,9H,ArH) ppm.MS:m/e 368(8), 351 (24) 338 (30), 322 (40), 321 (100), 307(6), 276(5), 247 (6), 229(40), 212(30), 200 (10), 199(50), 198(40), 183(30), 170(10), 127(10), 124 (16), 110(20).

Further elution with increasing concentration of chloroform gave 2–(3′–hydroxy–2′–methylphenoxy)–3–nitropyridine. Yield: 9.8 g (40%). Yellow crystals from cyclohexane–chloroform (50:50), m.p. 87–89° (Found: C, 58.47: H, 4.10; N, 11.41. Calc. for $C_{12}H_{10}N_2O_4$: C, 58.53; H, 4.06; N, 11.38%). IR: 3290, 1525, 1345, 1290, 1241 cm^{-1}. NMR: δ 2.1 (s, 3H, CH_3), 6.2–8.6 (m, 6H,ArH) and 7.8 (broad, IH, OH) ppm. The band at 7.8 ppm was replaced by a peak at 4.15 ppm on adding deuterated water. MS: m/e 246(30), 231(6), 230(4), 229(20), 228(15), 214(20), 213(10), 212(8), 211(13), 201(15), 200(70), 199(100), 198(55), 185(16), 183(8) 180(7), 171(12), 170(30), 142(12), 141(14), 137(18), 124(20), 123(16), 115(12) and 107(16).

Preparation of 2–(3'–Hydroxyphenoxy)–3–Nitropyridine (5a). 2–Chloro–3–nitropyridine was reacted with resorcinol as described in the above experiment. The product was extracted with ethyl acetate (2x100 ml), dried over anhyd. sodium sulphate and evaporated to dryness. The crude product was chromatographed over silica gel in cyclohexane/chloroform (1:1). The product thus separated was recrystallized from the same solvent; m.p. 72–75°. Yield: 6.2 g (53%) (Found: C, 56.6, H, 3.2; N, 12.4, Calc. for C_{11} H_8 N_2 O_4: C, 56.9 H, 3.4; N, 12.1%). IR: 3380, 1525, 1345, 1250, 1280 $cm.^{-1}$.

Preparation of 3–Hydroxy–2'–Nitrodipheny Sulphide (7). o-Chloronitrobenzene and thioresorcinol were prepared by the known procedures [3, 4]. 0.04M (6.3 g) *o*-chloronitrobenzene, 0.04M (5.0 g) thioresorcinol and sodium hydroxide (1.6 g) were mixed in 15 ml. dimethylformamide and heated at 100–120° for 1½ hr. The reaction mixture was cooled, acidified with 4N hydrochloric acid and extracted with ether. The ether extract was evaporated to dryness and the crude product was chromatographed on silica gel in ethyl acetate/benzene (1:4) when 3–hydroxy–2'–nitrodiphenyl sulphide was obtained as yellow crystals, m.p. 107°. Yield: 4 g (40%). (Found: C, 58.4; H, 3.7; N, 5.6. Calc. for C_{12} H_9 NO_3 S: C, 58.3; H, 3.6; N, 5.7%). IR: 3420, 1590, 1580, 1560, 1505 cm^{-1}. MS: m/e 247 (40), 230(25), 200(20), 184(15), 183(50), 182(30), 172(20), 171(40), 155(30), 155(100), 141(55), 139(25), 138(13), 131(10), 129(15), 128(20), 127(14), 115(18), 108(20), 93(30).

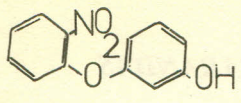
Preparation of 4–Carbomethoxy–3'–Hydroxy–2–Nitrodiphenyl Sulphide (8). 0.04M (8.6 g) methyl 4–chloro–3–nitrobenzoate, 0.04M (5 g) thioresosinol and sodium hydroxide (1.6 g) were stirred at 100–120° for 1½ hr. in 15 ml dimethylformamide. The reaction mixture was cooled, acidified with 4N hydrochloric acid and extracted with ether. The ether extract was dried over anhyd. sodium sulphate, evaporated to dryness and the crude product was chromatographed on silica gel, Elution with ethyl acetate/benzene (1:4) gave 4–carbomethoxy–3–hydroxy–2–nitrodiphenyl sulphide. R_f value: 0.838. Yield: 5.5 g (45%). Crystals from benzene, m.p. 150°. (Found: C, 49.9; H, 3.4; N, 4.8. Calc. for C_{13} H_{11} N O S: C, 49.7; H, 3.5; N, 4.6%). IR: 3420, 1590, 1580, 1560, 1505 cm^{-1} NMR: δ 3.65 (s, 3H, CH_3); 7.1–8.8 (m, 7H, Ar H) ppm.

Preparation of 6–Azaphenoxazin–3–one (9). 2–(3'–Hydroxyphenoxy)–3–nitropyridine (1 g) and ammonium chloride (0.5 g) were dissolved in 15 ml of 40% aqueous ethanol. Zinc dust (1.2 g) was added over a period of 15 min. The reaction mixture was stirred at 40–45° for further 30 min. The reaction mixture was filtered off the zinc oxide, washed with water and the filtrate diluted with water. The colourless filtrate was stirred in air for 6 hr when an orange coloured product was precipitated. This was extracted with chloroform, dried over anhyd, sodium sulphate and the solvent evaporated off. The product, 6–azaphenoxazin–3–one was purified by elution with chloroform/cyclohexane (40:60) over silica gel. Yield: 0.56 g (65%). Recrystalized from ethanol, m.p. 169-70°. IR: 1695, 1620 cm^{-1}. UV: λ_{max}. 330 (ϵ = 18200) and 446 (ϵ = 12930)nm.

Preparation of 6–Aza–4–Methylphenoxazin–3–One (10). 2–(3'–Hydroxy–2'–methylphenoxy)–3–nitropyridine was treated with zinc and ammonium chloride in the same way as described above and the product (yield 67%) was recrystalized from aqueous ethanol; m.p. 177–80°. (Found: C, 67.73; H, 3.47; N, 13.0 Calc. for C_{12} H_8 N_2O_2 C, 67.92; H, 3.77; N, 13.21%). IR: 1650, 1620, 1592, 1520, 1340, 1290 cm^{-1}. UV: λ_{max}. 330 (ϵ = 18000) and 446 (ϵ = 12930). NMR: δ 4.0 (s, 3H, CH_3), 6.5–8.6 (m.5H, ArH) ppm. MS: m/e 212 (100), 184(15), 156(12), 155(13), 129(12), 101(5) and 103(6).

Preparation of Phenothiazin–3–one (11). 3–Hydroxy–2'–nitrodiphenyl sulphide (1 g) was treated with zinc dust (1.2 g) and ammonium chloride (0.5g) as described above. The filtrate from the reaction mixture was stirred at room temperature for 4 hr. The orange red precipitate thus obtained was extracted with chloroform, dried over anhyd. sodium sulphate and the solvent evaporated. The crude product was chromatographed on silica gel in ethyl acetate/benzene (1:4) when phenothiazin–3–one was obtained in 80% yield (0.68 g). Crystals from benzene, m.p. 162° (lit, 160–165°). UV: $\lambda_{max.}$ 500 (ϵ = 15340), 365 (ϵ = 26400)nm. IR: 1638, 1605 cm^{-1} MS. m/e 213 (100), 185 (90).

Preparation of 8–Carbomethoxyphenothiazin–3–one (12). 8–Carbomethoxy–3'–hydroxy–2–nitrodiphenyl sulphide was reduced with zinc dust and ammonium chloride in 60% aqueous ethanol as described in the above procedure. The product obtained in 60% yield was recrystallized from benzene, mp. 169° (Found: C, 62.0; H, 3.3; N, 5.2. Calc. for C_{14} H_9 NO_3S:C, 61.9; H, 3.1; N, 5.6%). IR: 1638, 1606 cm^{-1}. UV: λ_{max} 475 (ϵ = 16,000), 345 (ϵ= 28,000)nm.



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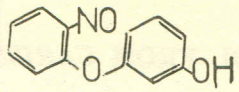

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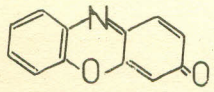

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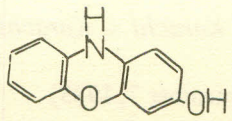

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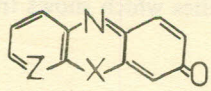

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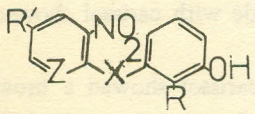

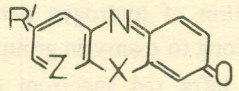

5a.	X=O;Z=N;R=R'=H	9. X=O;Z=N;R=R'=H
6.	X=O;Z=N;R=CH_3;R'=H	10. X=O;Z=N;R=CH_3;R'=H
7.	X=S;Z=C;R=R'=H	11. X=S;Z=C;R=R'=H
8.	X=S;Z=C;R=H;R'=CO_2CH_3	12. X=S;Z=C;R=H;R'=CO_2CH_3

RESULTS AND DISCUSSION

Earlier papers [5, 6] described a new synthetic route to 3H–phenoxazin–3–ones and related ring systems. The procedure was based upon the *in situ* generation of the nitroso species 2 by reaction of 1 with zinc and aqueous ammonium chloride and its subsequent cyclisation to 3. The reductive conditions employed also effected the subsequent conversion of 3 to 4 which readily changed back to 3 either by aerial oxidation or with ferric chloride and acetic acid. The work described in this paper involves synthesis of azaphenoxazin and phenothiazin–3–ones from 2–(3'–hydroxyphenoxy)–3–nitropyridines and 3–hydroxy–2' nitrodiphenyl sulphides respectively.

The necessary ethers (5a–8) were not reported in the literature, and they were readily obtained either by the reaction of 2–chloro–3–nitropyridine with potassium *m*–hydroxyphenoxides, or treatment of appropriate *o*-chloronitrobenzenes with mono-potassium salt of thioresorcinol [7]. Thus the treatment of 2–chloro–3–nitropyridine with *m*–hydroxyphenoxide in *N, N*–dimethylformamide containing cuprous oxide gave 2–(3'–hydroxyphenoxy)–3–nitropyridine (5a). In addition to satisfactory microanalysis the compound showed absorption bands at 3380, 1525 and 1345 cm^{-1} for hydroxyl and nitro groups respectively, whereas bands at 1280 and 1250 cm^{-1} were due to ether linkage. Reduction of (5) with zinc in aqueous ammonium chloride followed by aerial oxidation of the resulting colourless species gave an excellent yield of orange red 6–azaphenoxazinone (9). The compound not previously reported in the literature showed ultraviolet bands at 330 and 446 nm., and IR absorption bands at 1695 and 1620 cm^{-1} due to the quinonoid system. Similarly, 2–(3'–hydroxy–2'–methylphenoxy)–3–nitropyridine (6) reductively cyclised to 4–methyl–6–azaphenoxazinone (10) with remarkable ease which suggested that the procedure could be a convenient route to aza, di-aza or even tri-aza phenoxazinones.

Likewise, attempts to prepare the phenothiazinones from the appropriate thioethers proved highly successful. Thus 3–hydroxy–2'–nitrodiphenyl sulphide (7) readily cyclised to phenothiazinone (11), whereas, 8–carbomethoxy–3'–hydroxy–2–nitrodiphenyl sulphide (8) gave 8–carbomethoxyphenothiazinone (12). The latter compound not previously reported in the literature showed satisfactory microanalysis and was characterized further by IR and UV spectra. Thus IR absorption bands at 1638 and 1606 cm^{-1} and $\lambda_{max.}$ at 475 and 345 nm suggested characteristic quinonoid structure of the molecule.

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REFERENCES

1. C.O. Okafor, *Studies in the heterocyclic Series XII. The Chemistry and application of aza and thia analogs of phenoxazine and related compounds,* Heterocycles, **7**, (1), 391 (1977).
2. C.O. Okafor, *Studies in the heterocyclic series*–-III. The chemistry of azaphenothiazinone, Intern. J. Sulfur Chem. (8), **6**, 237 (1971).
3. H. Green and A.R. Day, J. Am. Chem. Soc., **64**, 1167 (1942); L.A. Elson, C.S. Gibson and J.D.A. Johnson, J. Chem. Soc., **2739** (1929).
4. E.R. Watson and S. Dutt, J. Chem. Soc., **2414** (1922).
5. C.W. Bird and M. Latif, Tetrahedron, **36**, 529 (1980).
6. C.W. Bird and M. Latif, Tetrahedron, **36**, 1813 (1980).
7. R.G.R. Bacon and O. J. Stewart, J. Chem. Soc., **4953** (1965).