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Proximity Effects in Diaryl Derivatives. Part V.[1] Syntheses of 2,7- and 2,8-Dichlorophenoxazine Derivatives. Smiles Rearrangements Activated only by Halogen Substituents

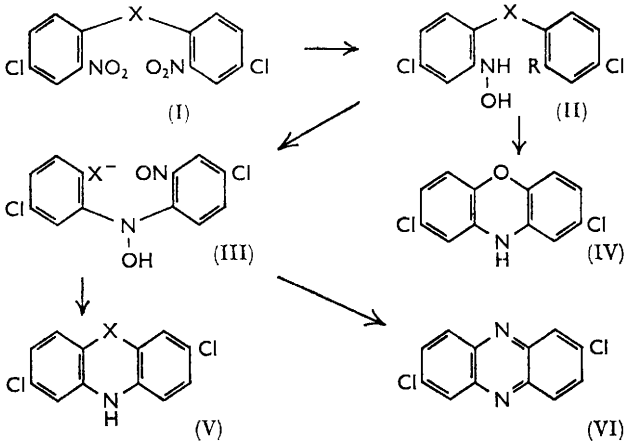
By M. F. Grundon and W. L. Matier

Syntheses of *N*-benzyl-2,7-dichlorophenoxazine and 2,8-dichlorophenoxazine show that the dichlorophenoxazine obtained [2] by reduction of 4,4'-dichloro-2,2'-dinitrodiphenyl ether with lithium aluminium hydride is the 2,8-isomer. The formation of this compound, therefore, does not involve a Smiles rearrangement.

Reaction of 2'-benzylamino-2,4',5-trichlorodiphenyl ether with potassium carbonate in dimethylformamide results in Smiles rearrangement to *N*-benzyl-2,8-dichlorophenoxazine, although the ring subject to nucleophilic attack is activated only by halogen substituents.

REDUCTION of 2,2'-dinitrodiaryl sulphones, *e.g.*, (I; X = SO_2), under alkaline conditions yields phenazines,[3] *e.g.*, (VI), and we have shown [4] that the probable intermediates are 2-hydroxyamino-2'-nitro- or -2'-nitroso-diaryl sulphones, *e.g.*, (II; X = SO_2, R = NO_2 or NO), which then undergo intramolecular nucleophilic rearrangement, (II) ⟶ (III), of the type investigated by Smiles and his collaborators.[5] 2,2'-Dinitrodiaryl ethers afford phenazines in a similar way. For example, reduction of 4,4'-dichloro-2,2'-dinitrodiphenyl ether (I; X = O) with lithium aluminium hydride at 20° furnished 2,7-dichlorophenazine (VI) (35%), but in this case a second product, $C_{12}H_7Cl_2NO$, was isolated in 9% yield.[2] This compound showed a single absorption peak in the NH region of the infrared spectrum, and was apparently a dichlorophenoxazine. If, by analogy with the sulphones, reduction of the ether (I; X = O) affords the 2-(hydroxyamino)diaryl ether (II; X = O, R = NO or NO_2) which subsequently rearranges to the phenazine (VI), then a dichlorophenoxazine could arise by displacement of a nitro- or a nitroso-substituent by the hydroxyamino-group. Alternative pathways are shown in the Scheme.

Direct displacement would yield 2,8-dichlorophenoxazine (IV), and displacement after rearrangement the 2,7-isomer (V; X = O). Reduction of the sulphide (I; X = S) gave 2,7-dichlorophenothiazine (V; X = S),[3] and this presumably arises by the latter pathway, (III) ⟶ (V). In order to further explore the mechanism of reduction in the ether series, the dichlorophenoxazine has been identified by synthesis; neither the 2,7- nor the 2,8-isomer has been prepared previously.



Scheme

For the synthesis of the 2,7-derivative we employed a modified Turpin procedure,[6] and obtained the 2,7-dichloronitrophenoxazine (X; R = NO_2) by reaction of the aminophenol (VII) with the chloronitro-derivative

[1] Part IV, M. F. Grundon, B. T. Johnston, and W. L. Matier, preceding Paper.

[2] M. F. Grundon and A. S. Wasfi, *J. Chem. Soc.*, 1963, 1982.

[3] Part III, M. F. Grundon and B. T. Johnston, *J. Chem. Soc.*(*B*), 1966, 255.

[4] M. F. Grundon, B. T. Johnston, and W. L. Matier, *Chem. Comm.*, 1965, 67.

[5] S. Smiles *et al.*, *J. Chem. Soc.*, 1931, 914, and succeeding Papers; J. F. Bunnett and R. E. Zahler, *Chem. Rev.*, 1951, **49**, 273.

[6] B. Boothroyd and E. R. Clark, *J. Chem. Soc.*, 1953, 1499.

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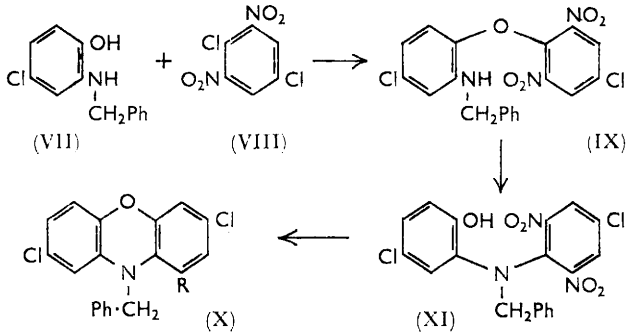
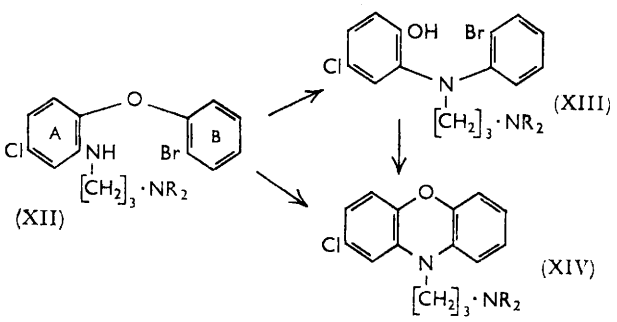
(VIII) in refluxing pyridine. After a shorter reaction time, a second product, $C_{19}H_{13}Cl_2N_3O_5$, was also isolated. This is the diphenylamine (XI) rather than the isomeric



ether (IX), since the chemical shifts for the OH and CH_2 protons appear as singlets when the n.m.r. spectrum is measured in [$^2H_6$]dimethyl sulphoxide; in this solvent OH and NH exchange is reduced,[7] and the NH and CH_2 resonances of the isomeric diaryl ether (IX) would be expected to appear as a triplet and as a doublet, respectively. Heating the diphenylamine (XI) with 1% sodium hydroxide afforded the 2,7-dichlorophenoxazine (X; R = NO_2) almost quantitatively. The isolation and cyclisation of the diphenylamine confirms that the synthesis of the phenoxazine is unambiguous, and shows that, although the diaryl ether (IX) may be an intermediate in the process,[8] its direct cyclisation (to a 2,8-dichlorophenoxazine) does not occur under the conditions of this reaction. Catalytic reduction of the nitrophenoxazine (X; R = NO_2) furnished the corresponding amine (X; R = NH_2). The primary amino-group was removed subsequently by diazotisation, followed by treatment of the diazonium salt with hypophosphorous acid. We were unable to debenzylate the resultant *N*-benzyl-2,7-dichlorophenoxazine (X; R = H), m. p. 128°, but this compound was clearly different from the isomer, m. p. 188°, obtained by benzylation of the dichlorophenoxazine derived by reduction of the dinitroether (I; X = O).

Phenoxazine has been prepared by cyclisation of 2,2′-diaminodiphenyl ether,[9] and the procedure was applied to the synthesis of 2,8-dichlorophenoxazine. Catalytic reduction of 4,4′-dichloro-2,2′-dinitrodiphenyl ether gave the corresponding diamine; heating an equimolecular mixture of the diamine and its dihydrochloride at 200° afforded 2,8-dichlorophenoxazine (IV), and this was identical with the compound, m. p. 206—207°, that was obtained [2] by reduction of 4,4′-dichloro-2,2′-dinitrodiphenyl ether (I; X = O) with lithium aluminium hydride. In the latter reaction, therefore, cyclisation to the phenoxazine must compete with the rearrangement, (II) ⟶ (III), that leads to the phenazine (VI). The intermediate (II) cannot yet be identified with certainty, but the 2-hydroxyamino-2′-nitrodiaryl ether (II; X = O, R = NO_2) is one possibility.

For the Smiles rearrangement of many *o*-aminodiaryl derivatives, strong activation by electron-attracting substituents in ring B [cf. (XII)] is usually considered essential. Many of the reactions are catalysed by strong bases, and the species >N$^-$ is believed to be the active nucleophil. In the special case of activated *o*-aminodiaryl ethers a strong base is not required, and rearrangement probably occurs through the un-ionised amino-group.[5] Bonvicino *et. al.*[10] showed recently, however, that the aminodiaryl ether (XII) rearranged to the diphenylamine (XIII), even though ring B was activated only by a halogen atom; the reagent employed ($NaNH_2$ in benzene) suggested that the nucleophil R–N$^-$ was involved. Reaction of the diphenylamine (XIII) with potassium carbonate in dimethylformamide afforded the phenoxazine (XIV), and this product was also obtained in the same way directly from the diaryl ether (XII). The latter reaction could proceed either *via* the diphenylamine (XIII) or by direct cyclisation, (XII) ⟶ (XIV). These authors favoured the latter course, since they considered that carbonate was an insufficiently strong base to effect an "unactivated" Smiles rearrangement. The characterisation of 2,7- and 2,8-dichlorophenoxazines described above provided an opportunity to reinvestigate this reaction.



Reaction of 2,5-dichlorophenol and 2,5-dichloronitrobenzene with sodium methoxide gave the diaryl ether (XV; R = NO_2), which was converted by catalytic reduction into the amine (XV; R = NH_2), further characterised as its hydrochloride. When the corresponding *N*-benzyl derivative (XVI) was refluxed with potassium carbonate in dimethylformamide, *N*-benzyl-2,8-dichlorophenoxazine (XVII) was obtained. This indicates that during the reaction rearrangement of the diaryl ether (XVI) to the diphenylamine (XVIII) occurred, followed by displacement of halogen; direct cyclisation of the aminodiaryl ether (XVI) would have furnished *N*-benzyl-2,7-dichlorophenoxazine (X; R = H). The aminodiaryl ether (XVI) possesses an extra halogen substituent in ring B, but in other respects is similar to the compound (XII) studied previously.[10]

[7] O. L. Chapman and R. W. King, *J. Amer. Chem. Soc.*, 1964, **86**, 1256.
[8] Cf. G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, *J. Org. Chem.*, 1961, **26**, 2797.
[9] M. P. Olmsted, P. N. Craig, J. J. Lafferty, A. M. Pavloff, and C. L. Zirkle, *J. Org. Chem.*, 1961, **26**, 1901.
[10] G. E. Bonvicino, L. H. Yogodzinski, and R. A. Hardy, *J. Org. Chem.*, 1962, **27**, 4272.

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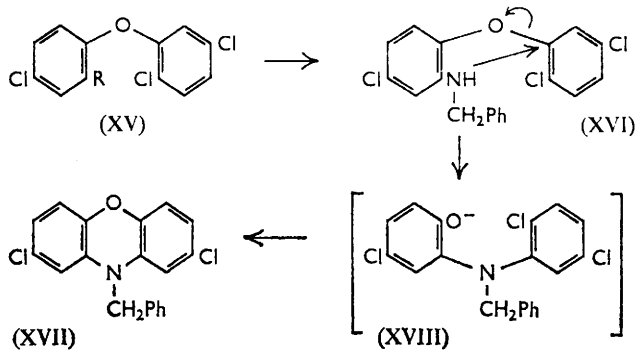
It now seems likely that the latter derivative also rearranges with carbonate in dimethylformamide before yielding the phenoxazine (XIV).



The extended investigations of Smiles and his collaborators,[5] and the kinetic studies of Bunnett and Okamoto [11] revealed many features of the Smiles rearrangement, but recent reports of unexpected rearrangements [2-4,10,12] show that certain aspects of the reaction are not yet fully understood, and suggest that a systematic kinetic investigation is now desirable.

EXPERIMENTAL

N-Benzyl-3,8-dichloro-1-nitrophenoxazine.—(*a*) A solution of *N*-benzyl-5-chloro-2-hydroxyaniline [6] (0·47 g.) and 1,4-dichloro-2,6-dinitrobenzene (0·47 g.) in pyridine (20 ml.) was heated at 100° for 30 min. Pyridine was removed *in vacuo*, and the residue in methylene chloride was washed successively with aqueous sodium hydroxide, with aqueous hydrochloric acid, and with water. The solvent was evaporated, and the residue in benzene was chromatographed on alumina. Elution with benzene gave the *phenoxazine*, separating from ethanol in red prisms (0·12 g., 16%), m. p. 127—128° (Found: C, 58·8; H, 3·0; N, 7·1. $C_{19}H_{12}Cl_2N_2O_3$ requires C, 58·9; H, 3·1; N, 7·2%). Elution with chloroform furnished *N-benzyl-4,5'-dichloro-2'-hydroxy-2,6-dinitrodiphenylamine* obtained from light petroleum (b. p. 60—80°) in orange needles (0·28 g.), m. p. 154—156° (Found: C, 52·1; H, 3·0; N, 9·7. $C_{19}H_{13}Cl_2N_3O_5$ requires C, 51·8; H, 2·9; N, 9·5%).

When the reaction mixture was heated for 6 hr., the phenoxazine was obtained in 35% yield.

(*b*) A solution of *N*-benzyl-4,5'-dichloro-2'-hydroxy-2,6-dinitrodiphenylamine (50 mg.) in 1% aqueous sodium hydroxide (10 ml.) was heated at 100° for 3 hr. The product was obtained with methylene chloride, and then chromatographed on alumina. Elution with benzene furnished the phenoxazine (40 mg., 91%), m. p. 128°.

1-Amino-N-benzyl-3,8-dichlorophenoxazine.—A solution of *N*-benzyl-3,8-dichloro-1-nitrophenoxazine (1·93 g.) in benzene (25 ml.) was reduced with palladium and hydrogen at 20° and at atmospheric pressure. The catalyst was removed, the solvent was evaporated, and the residue in benzene was chromatographed on alumina. Elution with benzene–light petroleum (b. p. 60—80°) (2 : 1) gave the *amine*, separating from ethanol in plates (1 g., 56%), m. p. 125—126° (Found: C, 63·9; H, 4·0. $C_{19}H_{14}Cl_2N_2O$ requires C, 63·9; H, 4·0%).

N-Benzyl-2,7-dichlorophenoxazine.— Concentrated sulphuric acid (1·1 ml.) in water (5 ml.) was added to 1-amino-*N*-benzyl-3,8-dichlorophenoxazine (2·3 g.) in acetic acid (10 ml.), and sodium nitrite (0·48 g.) in water (5 ml.) was added slowly to the stirred mixture at −5 to 0°. The solution was treated with ice-cold 50% hypophosphorous acid (10 ml.), kept at 0° for 48 hr., and then extracted with chloroform. The chloroform solution was washed with aqueous sodium carbonate and with water, and then evaporated. Chromatography of the residue on alumina, and elution with benzene furnished *N-benzyl-2,7-dichlorophenoxazine*, separating from light petroleum (b. p. 60—80°) in prisms (0·2 g., 9%), m. p. 127—128° (Found: C, 66·9; H, 3·9. $C_{19}H_{13}Cl_2N_2O$ requires C, 66·7; H, 3·8%).

2,2'-Diamino-4,4'-dichlorodiphenyl Ether.—A solution of 4,4'-dichloro-2,2'-dinitrodiphenyl ether (3·15 g.) in benzene (100 ml.) was reduced with palladium and hydrogen at 20° and at atmospheric pressure. Removal of the catalyst, evaporation of the solvent, and crystallisation of the residue from light petroleum (b. p. 60—80°) gave the *diamine* in needles (2·44 g., 92%), m. p. 124—126° (Found: C, 53·6; H, 3·8; N, 10·5. $C_{12}H_{10}Cl_2N_2O$ requires C, 53·6; H, 3·7; N, 10·4%).

2,8-Dichlorophenoxazine.—A mixture of 2,2'-diamino-4,4'-dichlorodiphenyl ether (0·54 g.) and its dihydrochloride (0·68 g.) (prepared by adding dry hydrogen chloride to a solution of the base in ether) was heated at 200—210° for 2·5 hr. in a sealed tube. Extraction with boiling benzene, chromatography of the extract on alumina, and elution with benzene gave *2,8-dichlorophenoxazine*, separating from light petroleum (b. p. 60—80°) in plates (40 mg., 8%), m. p. 205—206°, identical (mixed m. p. and infrared spectrum) with the dichlorophenoxazine, m. p. 206—207°, obtained [2] by reduction of 4,4'-dichloro-2,2'-dinitrodiphenyl ether with lithium aluminium hydride.

2,4',5-Trichloro-2'-nitrodiphenyl Ether.—A solution of 2,5-dichlorophenol (16·3 g.) and 2,5-dichloronitrobenzene (19·2 g.) in sodium methoxide [from sodium (3 g.) in methanol (100 ml.)] was evaporated, and the dry residue was heated at 190—200° for 10 hr. The product suspended in 10% aqueous sodium hydroxide (100 ml.) was extracted with ether. The ether was evaporated and the residue was extracted with boiling light petroleum (b. p. 60—80°). The light petroleum solution deposited the *diaryl ether*, which separated from the same solvent in yellow needles (15 g., 48), m. p. 67—69° (Found: C, 45·1; H, 2·0; N, 4·7. $C_{12}H_6Cl_3NO_3$ requires C, 45·2; H, 1·9; N, 4·4%).

2'-Amino-2,4',5-trichlorodiphenyl Ether and its Hydrochloride.—2'-Nitro-2,4',5-trichlorodiphenyl ether (6·37 g.) in chloroform (100 ml.) at 20° was reduced with palladium and hydrogen under atmospheric pressure. The catalyst was removed, the solvent was evaporated, and the residue in ether was treated with dry hydrogen chloride. The precipitate of the *hydrochloride* crystallised from ethanol–ether in needles (6·2 g., 95%), m. p. 139—141° (Found: C, 44·6; H, 2·9. $C_{12}H_9Cl_4NO$ requires C, 44·3; H, 2·8%).

Treatment of the hydrochloride with aqueous sodium carbonate yielded *2'-amino-2,4',5-trichlorodiphenyl ether*. Distillation at 162°/0·25 mm. gave an oil, which later formed crystals, m. p. 35—37° (Found: C, 50·0; H, 2·7; N, 4·7. $C_{12}H_8Cl_3NO$ requires C, 49·9; H, 2·8; N, 4·9%).

2'-Benzylamino-2,4',5-trichlorodiphenyl Ether and its Hydrochloride.—A mixture of 2'-amino-2,4',5-trichlorodiphenyl ether (1·45 g.), benzyl bromide (1·71 g.), sodium

[11] J. F. Bunnett and T. Okamoto, *J. Amer. Chem. Soc.*, 1956, **78**, 5363.
[12] E. A. Nodiff and M. Hausman, *J. Org. Chem.*, 1964, **29**, 2453.

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carbonate (0·6 g.), and t-butyl alcohol (25 ml.) was stirred and refluxed for 24 hr. Ether was added, the mixture was filtered, and the ether solution was evaporated. The residue in light petroleum (b. p. 60—80°) was treated with dry hydrogen chloride, and the precipitate of the *hydrochloride* crystallised from ether–methanol in needles (1·81 g., 96%), m. p. 101—104° (Found: C, 55·3; H, 3·8; N, 3·6. $C_{19}H_{15}Cl_4NO$ requires C, 55·0; H, 3·6; N, 3·4%).

Treatment of a portion of the hydrochloride with aqueous sodium carbonate gave the *base*, prisms (from methanol), m. p. 81—82° (Found: C, 60·0; H, 3·8; N, 4·0. $C_{19}H_{14}Cl_3NO$ requires C, 60·3; H, 3·7; N, 3·7%).

N-*Benzyl*-2,8-*dichlorophenoxazine*.—(*a*) Sodium was added to liquid ammonia until a blue solution was obtained. 2,8-Dichlorophenoxazine (217 mg.) was added, and the mixture was stirred for 1 hr., treated with benzyl iodide (0·4 g.), and stirring was continued until the ammonia evaporated. The residue in benzene was chromatographed on alumina. Elution with benzene afforded N-*benzyl*-2,8-*dichlorophenoxazine* separating from benzene–light petroleum (b. p. 60—80°) in needles (258 mg., 84%), m. p. 185—186° (Found: C, 66·8; H, 4·1. $C_{19}H_{13}Cl_2NO$ requires C, 66·7; H, 3·8%).

(*b*) A mixture of 2′-benzylamino-2,4′,5-trichlorodiphenyl ether hydrochloride (4·16 g.), potassium carbonate (4·2 g.), and dimethylformamide (50 ml.) was stirred and refluxed for 48 hr. After filtration, the solution was evaporated, and the product in benzene was chromatographed on alumina. Elution with benzene furnished *N*-benzyl-2,8-dichlorophenoxazine, crystallising from light petroleum (b. p. 60—80°) in needles (2·05 g., 60%), m. p. 185—186°, identical (mixed m. p. and infrared spectrum) with the sample obtained in (*a*).

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