RESEARCH PAPERS

DERIVATIVES OF DIPHENYL ETHER AS ANTITUBERCULOUS COMPOUNDS

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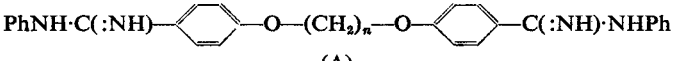
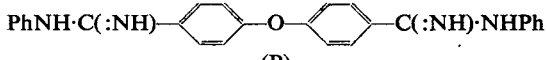
DERIVATIVES of diphenyl ether exhibit a remarkable range of biological activities; appropriate examples are afforded by thyroxine, alkaloids of the *Menispermaceæ* and *Berberidaceæ* and phenamidine. Appreciable activity *in vitro* against *Mycobacterium tuberculosis* has been observed in the depsidone, physodic acid,[1] in diploicin derivatives[2] and in a series of simple derivatives of diphenyl ether.[3]

Aromatic ethers containing the *N*-arylamidino group exhibit a highly specific antituberculous activity *in vitro* which is maintained in the presence of serum.[4,5] In the di-(4-*N*-arylamidinophenoxy)-alkanes[4] only compounds containing an odd number of atoms in the chain uniting the two phenyl nuclei (A; n = odd number) are active. Accordingly it appeared not unlikely that di-(4-*N*-arylamidino)-diphenyl ethers (B) would possess similar activity.



(A)



(B)

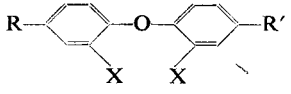
The *N*-arylamidino- and di-(*N*-arylamidino)-diphenyl ethers II, III, IV, V, VI, VIII and IX (Table I) were prepared by interaction of the appropriate arylammonium benzenesulphonate and nitrile.[6] No homogeneous product could be isolated in attempts to prepare 4:4′-di-(*N*-2-pyridylamidino)-diphenyl ether (VII) by the aluminium chloride method[7] but this compound was readily obtained by Pinner's method. 4:4′-Di-(2-benzimidazolyl)-diphenyl ether (X), a cyclic analogue of the diamidines, was prepared by fusion of 4:4′-dicyanodiphenyl ether with 2-aminophenylammonium toluene-4-sulphonate. When 4:4′-dicyanodiphenyl ether was brought into reaction with four equivalents of hydroxylamine, the main product was the corresponding diamidoxime (XI); the monoamidoxime (XII), formed with one equivalent of hydroxylamine, afforded the carbamidoamidoxime when treated with a further equivalent of hydroxylamine in aqueous ethanol. For the formation of the oxygen isosteres of the diamidines, 4:4′-di(*N*-phenylcarbamido)-diphenyl ether (XIV) and 4:4′-di-(*N*-2-pyridylcarbamido)-diphenyl ether (XV), aniline and 2-aminopyridine respectively were acylated with 4:4′-dichloroformyldiphenyl ether.

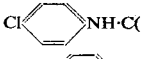
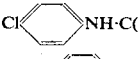
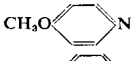
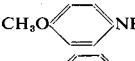
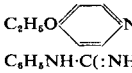
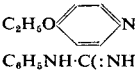
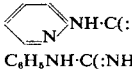
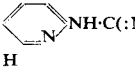
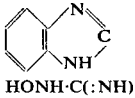
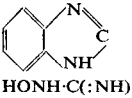
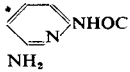
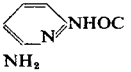
ANTITUBERCULOUS ACTIVITY

The activities of the compounds tested are listed in Table I. As was anticipated, the di-(4-*N*-arylamidino)-diphenyl ethers were highly active in the presence of serum. The effects of substituents in the *N*-aryl group in causing a decrease in activity were similar to those observed in the di-(4-*N*-arylamidinophenoxy)alkanes[4] except in the case of the 4-chloro compound (III); in the present series the decrease in activity was considerably less marked. Isosteric replacement of the *N*-phenylamidino groups of compound II by *N*-2-pyridylamidino (VII) or 2-benzimidazolyl (X) groups produced a considerable fall in activity; this effect was even more evident in the oxygen isosteres XIV and XV.

TABLE I

ANTITUBERCULOUS ACTIVITIES OF DIPHENYL ETHER DERIVATIVES



No.	R	R′	X	Activity*
I	$NH_2{\cdot}C(:NH)$	$NH_2{\cdot}C(:NH)$	H	5†
II	$C_6H_5NH{\cdot}C(:NH)$	$C_6H_5NH{\cdot}C(:NH)$	H	100
III			H	50
IV			H	50–100
V			H	50
VI	$C_6H_5NH{\cdot}C(:NH)$	$C_6H_5NH{\cdot}C(:NH)$	I	10
VII			H	10
VIII	$C_6H_5NH{\cdot}C(:NH)$	H	H	50–100
IX	$C_6H_5NH{\cdot}C(:NH)$	CH_3O	H	81
X			H	5
XI	$HONH{\cdot}C(:NH)$	$HONH{\cdot}C(:NH)$	H	9
XII	$HONH{\cdot}C(:NH)$	CN	H	5
XIII	COOH	COOH	H	<1
XIV	C_6H_5NHOC	C_6H_5NHOC	H	<1
XV			H	1
XVI	NH_2	NH_2	H	<1

* Dilution in thousands at which complete inhibition of the growth of *M. tuberculosis* (human virulent strain) was maintained for 4 weeks in modified Long's medium (by the floating pellicle method) in the presence of 10 per cent. of serum.

† Tested in the absence of serum.

The foregoing and other structural variations recorded in Table I, all of which led to a decrease in activity, bear little resemblance, where comparison is possible, to the relationships between structure and activity observed by Barry *et al.*[3] in other derivatives of diphenyl ether. Further evidence on the specific effect of the *N*-aryl group, additional to that illustrated by the relative activities of compounds I and II, is afforded

by a comparison of the activity of compound VIII with that of the corresponding unsubstituted amidine (VIII; R = $NH_2 \cdot C(:NH)$; R′ = X = H) prepared by Barry *et al.*[3]; employing a similar method of testing they found this compound to be active at 1 to 10,000.

With compound II some evidence of activity *in vivo* in guinea-pigs was obtained but its toxicity was relatively high. Although compound III had a considerably lower acute toxicity, no activity *in vivo* could be demonstrated because of its high chronic toxicity.

EXPERIMENTAL

4:4′-*Di*-(N-*phenylamidino*)-*diphenyl ether* (II). 4:4′-Dicyanodiphenyl ether[8] (10 g.) and phenylammonium benzenesulphonate (22·6 g., 2 mols.) were heated together, with occasional stirring, in a refluxing nitrobenzene bath (210° C.) for 1 hour. A solution of the cooled melt in ethanol (250 ml.) on pouring into 5 N sodium hydroxide (30 ml.) and crushed ice (100 g.) afforded 4:4′-di-(*N*-phenylamidino)-diphenyl ether which crystallised as leaflets, m.pt. 207° to 208° C., from ethanol; yield 14 g. (69 per cent.). Found: N, 13·8; $C_{26}H_{22}ON_4$ requires N, 13·8 per cent. The dibenzenesulphonate crystallised from methanol in prisms, m.pt. 186° to 188° C. Found: N, 7·5; $C_{38}H_{34}O_7N_4S_2$ requires N, 7·75 per cent.

The following diamidines were similarly prepared from 4:4′-dicyanodiphenyl ether and the appropriate arylammonium benzenesulphonate.[4]

4:4′-*Di*-N-4-*chlorophenylamidino*)-*diphenyl ether* (III). Needles, m.pt. 190° to 190·5° C. with slight decomposition, from ethanol; yield 91 per cent. Found: N, 11·8; $C_{26}H_{20}ON_4Cl_2$ requires N, 11·8 per cent. The dibenzenesulphonate, rosettes of needles from ethanol, had m.pt. 284° to 285° C. Found: N, 6·8; $C_{38}H_{32}O_7N_4S_2Cl_2$ requires N, 7·1 per cent.

4:4′-*Di*-(N-4-*methoxyphenylamidino*)-*diphenyl ether* (IV). Leaflets, m.pt. 231° to 232° C., from ethanol; yield 50 per cent. Found: N, 11·7; $C_{28}H_{26}O_3N_4$ requires N, 12·0 per cent. The dipicrate crystallised as needles, m.pt. 181° to 183° C. with decomposition, from acetic acid. Found in material dried at 110° C. *in vacuo*: C, 51·8; H, 3·8; $C_{40}H_{32}O_{17}N_{10}$ requires C, 51·9; H, 3·5 per cent.

4:4′-*Di*-(N-4-*ethoxyphenylamidino*)-*diphenyl ether* (V). Leaflets, m.pt. 238° to 239° C., from ethanol. Found: N, 11·2; $C_{30}H_{30}O_3N_4$ requires N, 11·3 per cent. The monopicrate crystallised as orange plates, m.pt. 208° to 210° C., from ethanol. Found, in material dried at 110° C. *in vacuo*: N, 13·7; $C_{36}H_{33}O_{10}N_7$ requires N, 13·6 per cent.

2:2′-*Diiodo*-4:4′-*di*-(N-*phenylamidino*)-*diphenyl ether* (VI). The product obtained when 2:2′-diiodo-4:4′-dicyanodiphenyl ether[9] (3·7 g.) and phenylammonium benzenesulphonate (4 g.; 2 mols.) were heated together at 210° C. for 2 hours was dissolved in ethanol (50 ml.); basic material was extracted with aqueous lactic acid from the precipitate formed on adding the ethanol solution to aqueous ammonia, and purified by crystallisation from ethanol. Yield 2·8 g. (54 per cent.). Prisms, m.pt. 246° to 247° C. Found: C, 47·6; H, 3·2; N, 8·5; $C_{26}H_{20}ON_4I_2$ requires C, 47·4; H, 3·0; N, 8·5 per cent.

4:4′-*Di*-(N-2-*pyridylamidino*)-*diphenyl ether* (VII). A suspension of finely powdered 4:4′-dicyanodiphenyl ether (10 g.) in absolute ethanol (70 ml.) was saturated with dry hydrogen chloride at 0° C. and shaken for 2 days. After keeping a further 7 days most of the solid had dissolved. The solvent was removed *in vacuo* and 2-aminopyridine (25·6 g.) dissolved in absolute ethanol (50 ml.) was added. The semi-solid mass, obtained after keeping for 3 days, on crystallisation from a mixture of *iso*propanol and dilute hydrochloric acid, afforded the dihydrochloride trihydrate as prisms, m.pt. 196° to 198° C. after sintering at 180° C. Yield 20 g. (82 per cent.). Found: C, 53·7; H, 5·1; H_2O (Karl Fischer), 10·6; $C_{24}H_{20}ON_6,2HCl,3H_2O$ requires C, 53·8; H, 5·2; H_2O, 10·1 per cent. 4:4′-Di-(*N*-2-pyridylamidino)-diphenyl ether crystallised from ethanol as fine needles, m.pt. 207° to 208° C. with decomposition. Found: C, 70·7; H, 4·8; N, 20·8; $C_{24}H_{20}ON_6$ requires C, 70·6; H, 4·9; N, 20·6 per cent. The dipicrate monohydrate crystallised as needles, m.pt. 213° to 214° C. after sintering at 147° to 150° C., from aqueous acetic acid. Found: N, 19·0; loss at 110° C. *in vacuo*, 2·5; $C_{36}H_{26}O_{15}N_{12},H_2O$ requires N, 19·0; H_2O, 2·0 per cent.

4-N-*Phenylamidinodiphenyl ether* (VIII). This was prepared in the usual way from 4-cyanodiphenyl ether[9] and phenylammonium benzenesulphonate and purified as its benzenesulphonate which crystallised as prisms, m.pt. 157° to 158° C., from water. Yield 84 per cent. Found in material dried at 110° C. *in vacuo*: N, 6·4; $C_{25}H_{22}O_4N_2S$ requires N, 6·3 per cent. The base crystallised as leaflets, m.pt. 139° to 140° C., from light petroleum (b.pt. 100° to 120° C.). Found: N, 9·9; $C_{19}H_{16}ON_2$ requires N, 9·7 per cent.

4-(4-*Methoxyphenoxy*)-N-*phenylbenzamidine* (IX). This was prepared from 4-(4-methoxyphenoxy)-benzonitrile[10] and phenylammonium benezenesulphonate in the manner described for compound VI and obtained as leaflets, m.pt. 130° to 131° C., from light petroleum (b.pt. 100° to 120° C.). Found: N, 9·1; $C_{20}H_{18}O_2N_2$ requires N, 8·8 per cent. The benzenesulphonate crystallised as prisms, m.pt. 158° to 159° C., from *iso*propanol. Found: N, 6·0; $C_{26}H_{24}O_5N_2S$ requires N, 5·9 per cent.

4:4′-*Di*(2-*benzimidazolyl*)-*diphenyl ether* (X). When 4:4′-dicyanodiphenyl ether (4·4 g.) and 2-aminophenylammonium toluene-4-sulphonate (11·2 g.; 2 mols.) were heated together at 210° C. an exothermic reaction occurred; after this had subsided (20 minutes) the resulting solid was heated at 210° C. for 15 minutes. The cooled product, after extraction with hot water to remove ammonium toluene-4-sulphonate, was dissolved in aqueous lactic acid and the crude base, m.pt. 350° to 354° C., liberated by ammonia, was crystallised as leaflets from nitrobenzene. 4:4′-Di-(2-benzimidazolyl)-diphenyl ether had m.pt. above 360° C. Yield 5 g. (62 per cent.). Found: N, 14·0; $C_{26}H_{18}ON_4$ requires N, 13·9 per cent. Its monopicrate crystallised from aqueous cellosolve as needles, m.pt. 285° to 287° C. with decomposition. Found in material dried at 110° C. *in vacuo*: N, 15·7; 15·6; $C_{32}H_{21}O_8N_7$ requires N, 15·5 per cent.

4:4′-*Diamidoximinodiphenyl ether* (XI). (*a*) 4:4′-Dicyanodiphenyl

ether (11 g.) was dissolved in ethanol (500 ml.) and a solution of hydroxylamine in water (30 ml.) prepared from the hydrochloride (7 g.; 2 mols.) and sodium carbonate (5·3 g.; 1 mol.) was added. The mixture was refluxed for 28 hours, filtered and evaporated to about 50 ml. The solid which separated was repeatedly crystallised from aqueous ethanol and afforded 4-(4-cyanophenoxy)-benzamidoxime (XII) as prisms, m.pt. 196° to 197° C., with decomposition. Yield 5·3 g. (42 per cent.). Found: C, 66·5; H, 4·5; N, 16·3; $C_{14}H_{11}O_2N_3$ requires C, 66·4; H, 4·4; N, 16·6 per cent. 4-(4-Cyanophenoxy)-benzamidoxime on refluxing for 24 hours with aqueous ethanolic hydroxylamine (2 mols.) gave 4-(4-carbamidophenoxy)-benzamidoxime which crystallised from aqueous *iso*propanol as plates, m.pt. 172° to 173° C., with decomposition. Found: N, 15·4; $C_{14}H_{13}O_3N_3$ requires N, 15·5 per cent.

(*b*) The dinitrile (11 g.) and hydroxylamine (8 mols.) were heated together in aqueous ethanol at 65° to 70° C. for 24 hours. The crude product, obtained as described above, after repeated crystallisation from aqueous *iso*propanol yielded 4:4′-diamidoximinodiphenyl ether as prisms, m.pt. 193° to 194° C., with decomposition, depressed to 178° to 180° C. on admixture with 4-(4-cyanophenoxy)-benzamidoxime. Yield 3 g. (21 per cent.). Found: C, 58·5; H, 4·9; N, 19·7; $C_{14}H_{14}O_3N_4$ requires C, 58·7; H, 4·9; N, 19·6 per cent.

No improvement in the yield was effected by carrying out the reaction in absolute ethanol using a solution of hydroxylamine prepared from the hydrochloride and sodium ethoxide or triethylamine.

4:4′-*Dichloroformyldiphenyl ether.* 4:4′-Dicyanodiphenyl ether on boiling with sulphuric acid (70 per cent.) for 3 hours afforded 4:4′-dicarboxydiphenyl ether (XIII) which crystallised as prisms, m.pt. 328° to 330° C., from acetic acid. Yield 85 per cent. Found: Eq. wt., 132; required, 129. Schickh[11] records no melting point for this acid. The dicarboxylic acid (21·5 g.) and thionyl chloride (41 ml.) were refluxed together for 4 hours. The excess of thionyl chloride was removed under reduced pressure and the residue was crystallised from light petroleum (b.pt. 100° to 120° C.); prisms, m.pt. 82° to 83° C. Found: C, 57·3; H, 2·9; $C_{14}H_8O_3Cl_2$ requires C, 57·0; H, 2·7 per cent.

4:4′-*Di*-(N-*phenylcarbamido*)-*diphenyl ether* (XIV). This was prepared from the diacyl chloride described above and aniline under Schotten–Baumann conditions and crystallised from acetic acid as leaflets, m.pt. 297° to 299° C. Found: N, 6·9; $C_{26}H_{20}O_3N_2$ requires N, 6·9 per cent.

4:4′-*Di*-(N-2-*pyridylcarbamido*)-*diphenyl ether* (XV). 4:4′-Dichloroformyldiphenyl ether (7·7 g.) and 2-aminopyridine (7·5 g.) were boiled together in dry benzene (60 ml.) for 30 minutes; the solvent was evaporated and the residue was extracted first with water and then with dilute hydrochloric acid. The base liberated by ammonia crystallised from ethanol as prisms, m.pt. 181° to 182° C. Yield 4 g. (32 per cent.). Found: N, 13·4; $C_{24}H_{18}O_3N_4$ requires N, 13·7 per cent.

4:4′-*Diaminodiphenyl ether* (XVI). 4:4′-Dinitrodiphenyl ether, reduced in acetic acid with stannous chloride and hydrochloric acid, afforded

the diamine in 85 per cent. yield. This by interaction with benzenesulphonic acid in water gave the dibenzenesulphonate which crystallised from methanol as needles, m.pt. 286° to 288° C., with decomposition. Found: N, 5·5; $C_{24}H_{24}O_7N_2S_2$ requires N, 5·4 per cent.

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SUMMARY

1. A number of derivatives of diphenyl ether have been prepared for examination of their antituberculous activity.

2. Some evidence of activity *in vivo* was obtained with 4:4′-di-(*N*-phenylamidino)-diphenyl ether but the compound was toxic.

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