Synthesis and antimicrobial activity of 2-substituted-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxides

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A series of 2-aryloxyl-2-arylthio-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxides 3 have been synthesized by reacting 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol 1 with different arylphosphorodichloridates 2 in the presence of triethylamine at 70-80°C. Some of these compounds are prepared by reacting the monochloride, 2-chloro-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxide 4, in situ with substituted phenol and thiols 5. The monochloride is prepared by condensing 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol with phosphorus oxychloride. IR, 1H, 13C and 31P NMR and mass spectral data have been discussed. Some of these compounds have been screened for their antibacterial and antifungal activities.

Large number of organophosphorus esters are being used as pesticides and insecticides. The observation that several saligenin cyclic phosphates have a biologically active metabolite of tri-O-tolylophosphate led to the synthesis of many related compounds.

In our endeavour to develop high potency pesticides, a series of 2-aryloxyl/arylthio-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxides 3a-h, which are analogous to the saligenin cyclic phosphates, were prepared by the condensation of equimolar quantities of 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol 1 with various aryl phosphorodichloridates 2 in dry toluene in the presence of triethylamine at 70-80°C (Scheme I). However, compounds 3i-1 (cf. Tables I and II) were prepared by an alternative route by the reaction of the monochloride, 2-chloro-6-chloro-8-nitro-4-trichloromethyl)-4H-1,3,2-benzodioxaphosphorin 2-oxide 4 with various substituted thiols and phenol since the corresponding dichloridates could not be prepared due to their thermal decomposition during vacuum distillation. The monochloride was obtained by condensing 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol with phosphorus oxychloride in the presence of triethylamine in dry toluene. Their structures were established by elemental analyses, IR, 1H, 13C and 31P NMR and mass spectral data.

Antimicrobial activity

Some of the compounds were screened for their antifungal activity in vitro against the fungi Aspergillus niger and Curvularia lunata using the fungicide Griseofulvin as standard. Griseofulvin exhibited a zone of inhibition of 100% against both fungi Aspergillus niger and Curvularia lunata. The culture media was PDA and the method employed was disc...
Table I—Characterization, IR and EI mass spectral data of 2-arylxy/arylthio-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxides 3

<table>
<thead>
<tr>
<th>Compd</th>
<th>m.p. °C</th>
<th>Mol. formula</th>
<th>IR(^{31}) (ν(_{max}), cm(^{-1}))</th>
<th>P-O</th>
<th>P-O-C (alom.)</th>
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<tbody>
<tr>
<td>3a</td>
<td>166-67</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1305 1200, 980</td>
<td>1160</td>
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<tr>
<td>3b</td>
<td>194-95</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1296 1245, 974</td>
<td>1176</td>
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<tr>
<td>3c</td>
<td>172-73</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
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<tr>
<td>3d</td>
<td>210-11</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1282 1201, 972</td>
<td>1166</td>
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<tr>
<td>3e</td>
<td>220-21*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1310 1205, 990</td>
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<tr>
<td>3f</td>
<td>188-89</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1284 1237, 977</td>
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<td>3g</td>
<td>151-52</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1300 1205, 985</td>
<td>1175</td>
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<tr>
<td>3h</td>
<td>134-35*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1310 1245, 980</td>
<td>1185</td>
<td></td>
</tr>
<tr>
<td>3i</td>
<td>116-17*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1300 630 (P-S), 535 (S-C)</td>
<td>1175</td>
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<tr>
<td>3j</td>
<td>122-23*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1305 603 (P-S), 540 (S-C)</td>
<td>1170</td>
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<tr>
<td>3k</td>
<td>132-33*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1295 625 (P-S), 525 (S-C)</td>
<td>1165</td>
<td></td>
</tr>
<tr>
<td>3l</td>
<td>202-03*</td>
<td>C(_2)H(_3)ClNO(_3)P</td>
<td>1280 1245, 995</td>
<td>1180</td>
<td></td>
</tr>
</tbody>
</table>

\(^1\)Recrystallized from 2-propanol.
\(^2\)Recrystallized from chloroform-hexane.
\(^3\)Recrystallized from aqueous 2-propanol.

3d, MS: m/z 479 [(M+8\(^{39}\)), 2], 477 [(M+6\(^{39}\)), 5], 475 [(M+4\(^{39}\)), 15], 473 [(M+2\(^{39}\)), 20], 471[M\(^{39}\), 14], 383 (15.5), 381 (10), 264 (35), 248 (46.5), 219 (20), 203 (18.5), 188 (100), 170 (20), 154 (33.5), 108 (92), 107 (50).

3e, MS: m/z 493 [(M+8\(^{39}\)), 2], 491 [(M+6\(^{39}\)), 6], 489 [(M+4\(^{39}\)), 15], 487 [(M+2\(^{39}\)), 21], 485 (M\(^{39}\), 15), 452 (5), 421 (5), 386 (15), 368 (50), 359 (15), 303 (10), 288 (18), 269 (44), 232 (33), 220 (06), 202 (100), 186 (35), 157 (50), 122 (75), 97 (47).

Table II—\(^1\)H, \(^13\)C and \(^31\)P NMR data of 3

<table>
<thead>
<tr>
<th>Compd</th>
<th>(^1)H NMR(^{12})</th>
<th>(^13)C NMR(^{15-17})</th>
<th>(^31)P NMR(^{18-20})</th>
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</thead>
</table>
| 3a    | δ 6.36 (d, 9.9, 1H, 4-CH), 8.03 (d, 2.8, 1H, 5-CH), 8.20 (d, 2.8, 1H, 7-CH), 6.98, 7.20, 7.65 (OAr-H) | 87.7 (8.1, C-4), 131.1 (C-5), 131.8 (C-6), 127.7 (C-7), 129.1 (C-8), 148.5 (7.1, C-9), 117.3 (C-10), 98.2 (C-11), 139.2 (C-1'), 121.8 (C-2'), 128.3 (C-3'), 125.1 (C-4'), 128.3 (C-5'), 121.8 (C-6') |△H\(_3\)PO\(_4\) (85%)

Table II (contd)
Experimental Section

General. Melting points were determined on a Mel-Temp apparatus and are uncorrected. Microanalyses were performed at RSIC, Central Drug Research Institute, Lucknow. IR spectra ($\nu_{\text{max}}$ in cm$^{-1}$) were recorded in KBr on a Perkin-Elmer 683 spectrophotometer. $^1$H and $^{13}$C NMR spectra were recorded on Varian XLAA-300 and XLAA-400 spectrometers operating at 300 and 400 MHz respectively for $^1$H and at 75 and 101 MHz respectively for $^{13}$C, while $^{31}$P NMR spectra were taken on a Varian XLAA-400 spectrometer operating at 162 MHz using 85% H$_3$PO$_4$ as external standard. All NMR spectra were taken in CDCl$_3$ or DMSO-$d_6$ solutions and were referenced from TMS ($^1$H and $^{13}$C, chemical shifts in $\delta$). Mass spectra were recorded on an AUTO SPEC Q instrument using solid probe at 70 eV.

2- (2,2,2-Trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol 1. To a cooled solution of 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol (5.52 g, 0.02 mole) in acetic acid (100 mL) was added dropwise a solution of nitric acid (1.4 mL, 0.015 mole) in acetic acid (25 mL) during 20 min at 20°C. The reaction mixture was further stirred for 3 hr at room temperature. Progress of the reaction was followed by TLC analysis. The reaction mixture was poured into ice water. During the addition of ice water a yellow precipitate of 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol separated. It was recrystallised from the mixture of ethyl acetate-hexane to give 1 as yellow crystals, yield 4.95 g (77%), mp 146-147°C.

2- (4-Methylphenoxy)-6-chloro-8-nitro-4-trichloromethyl-4H-1, 3, 2-benzodioxaphosphorin 2-oxide 3d. A solution of 4-methylphenyl phosphochloridate 2d (1.12 g, 0.005 mole) in dry toluene (10 mL) was added dropwise over a period of 15 min. to a stirred solution of 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol 1 (1.61 g, 0.005 mole) and triethylamine (1.01 g, 0.01 mole) in dry
toluene (60 mL) at room temperature. After the addition was over, the stirring was continued for 6-7 hr at 70-80°C. Progress of the reaction was followed by TLC analysis. Triethylamine hydrochloride was filtered off and the solvent from the filtrate was evaporated under reduced pressure. The crude product 3d was washed with water and recrystallized from 2-propanol to give yellow crystals yield 1.48 g (63%), mp 210-11°C. Compounds 3a-h were synthesized by the above procedure.

2- (Thiophenoxy)-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxide 3i.

To the stirred solution of 2- (2,2,2-trichloro-1-hydroxyethyl)-4-chloro-6-nitrophenol 1 (1.61 g, 0.005 mole) and triethylamine (1.01 g, 0.01 mole) in dry toluene (50 mL) was added a solution of phosphorus oxychloride (0.76 g, 0.005 mole) in toluene (15 mL) during 15 min. at 0-5°C. The reaction mixture was warmed and the reaction continued for 4 hr to give the monochloride, 2-chloro-6-chloro-8-nitro-4-trichloromethyl-4H-1,3,2-benzodioxaphosphorin 2-oxide 4 which was cooled and subsequently added to it a solution thiophenol 5i (0.55 g, 0.005 mole) and triethylamine (0.50 g, 0.005 mole) in dry toluene (20 mL) and stirring continued for another 5 hr at 45-50°C. The triethylamine hydrochloride was filtered and the filtrate evaporated. The residue was washed with water, dried and recrystallized from the aqueous 2-propanol to give pure compound 3i, yield 1.42 g (60%), mp 116-17°C.

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References