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Synthesis and Reactions of Some 4′-(2-Pentachlorophenoxy-ethoxy) Substituted Chalcones

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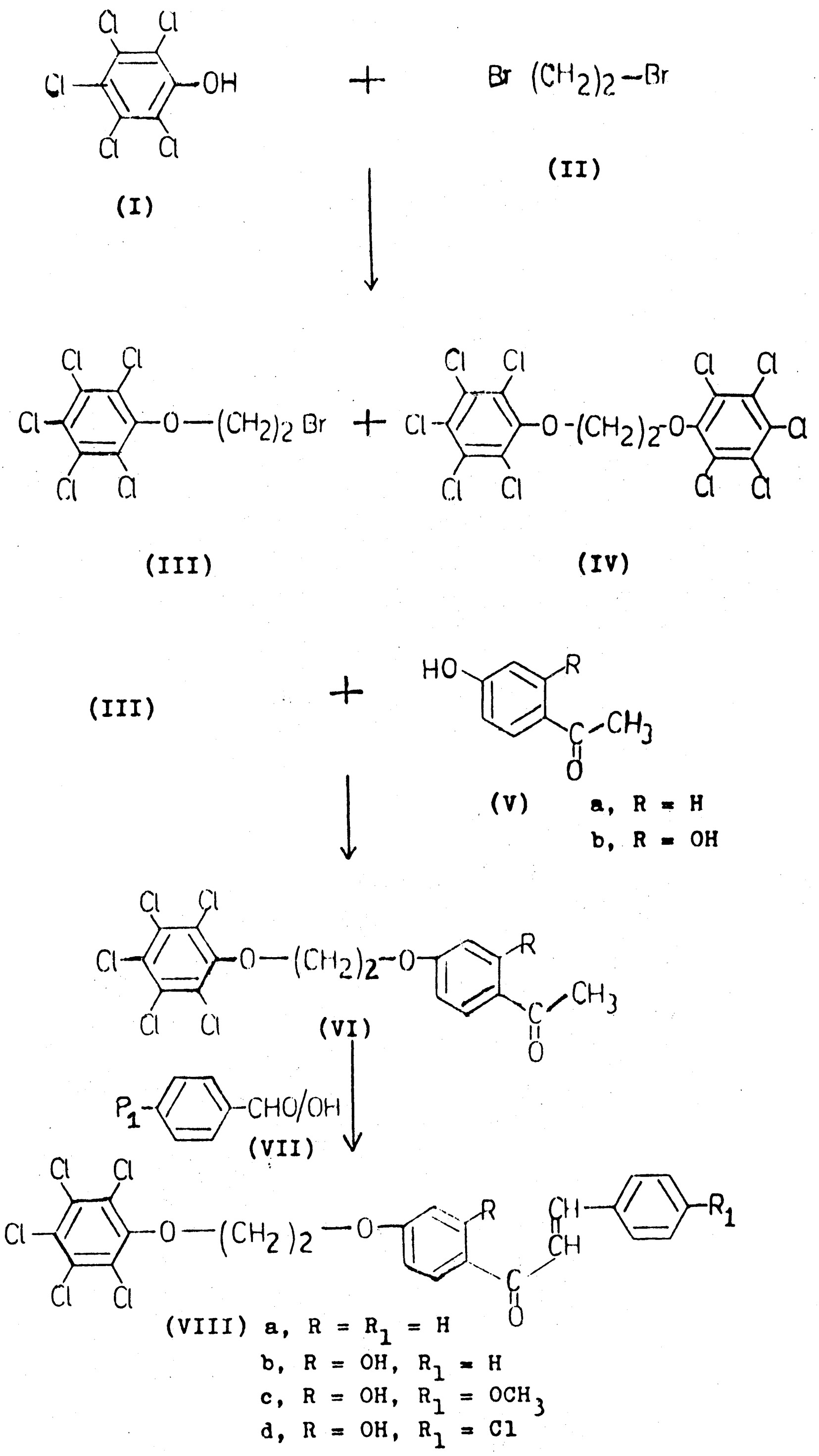
Reaction of pentachlorophenol with 1,2-dibromoethane gave a mixture of 2-(pentachlorophenoxy)-ethylbromide(III) and 1,2-bis-(pentachlorophenoxy)-ethane (IV) which were separated as aceton soluble (III) and insoluble (IV) components. Reaction of (III) with *p*-hydroxyacetophenone (Va) and resacetophenone (Vb) resulted 4-(2-pentachlorophenoxy ethoxy)-acetophenone (VIa) and 2-hydroxy-4-(2-pentacholorophenoxy ethoxy)–acetophenone (VIb) respectively. Condensation of VIa and VIb with *p*-substituted aromatic aldehydes (VII) afforded the corresponding chalcones (VIII). Compound (VIIIb) was treated with DMSO and iodine, bromine in acetic acid and alkaline hydrogen peroxide to afford flavone (IXa), dibromochalcone (X) and flavonol (IXb) derivatives. The structures of the synthesised compounds have been established on the basis of elemental analysis and spectral data. Some of the synthesised compounds were found to be active against number of micro-organisms.

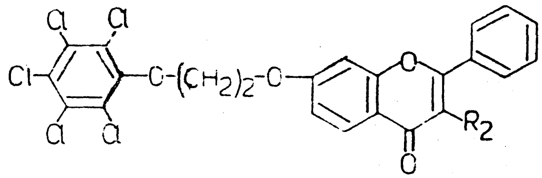
INTRODUCTION

Chalcones are potential biocides because some naturally occurring antibiotics and amino chalcones[1] probably owe their biological activity to the presence of α, β-unsaturated carbonyl group[2]. Chalcones and their analogues are used as bactericides[3], germicides[4], insecticides[5] and antifertility agents[6]. In view of this in the present investigation we have synthesised some new 4′-(2-pentachlorophenoxy ethoxy) substituted chalcones and these in turn have been transformed to different derivatives. Some of these compounds (IV, Va, VIb, VIIIb–d) have shown interesting biological activities against a number of micro-organisms.

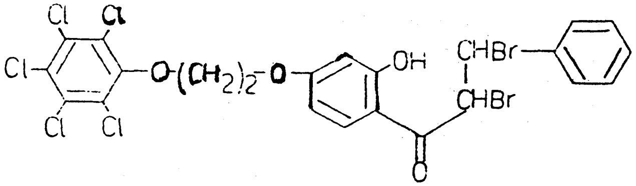
RESULTS AND DISCUSSION

For the synthesis[7,8] of compounds (VIII) listed above pentachlorophenol (I) was treated with 1,2-dibromoethane (II) in the molar ratio of 1 : 1 in presence of anhydrous K_2CO_3 and dry acetone. The reaction mixture after purification was separated into acetone-soluble and insoluble components. The acetone-soluble compound was characterized as 2-(pentachlorophenoxy)-ethyl bromide (III) and the insoluble one as 1,2-bis-(pentachlorophenoxy)-ethane (IV). IR spectrum of


(I)
(II)
(III)
(IV)
(III)
(V) a, R = H
b, R = OH
(VI)
(VII)
(VIII) a, R = R1 = H
b, R = OH, R1 = H
c, R = OH, R1 = OCH3
d, R = OH, R1 = Cl



(IX) a, R_2 = H
b, R_2 = OH



(III) showed characteristic bands in the regions 1220 (C—O—C asymmetric) and 1020 cm^{-1} (C—O—C symmetric).

The above bromo intermediate (III) was refluxed in presence of acetone and anhydrous K_2CO_3 with *p*-hydroxyacetophenone (Va) and resacetophenone (Vb) to afford 4-(2-pentachlorophenoxy ethoxy)-acetophenone (VIa) and 2-hydroxy-4-(2-pentachlorophenoxy ethoxy)-acetophenone (VIb) respectively. IR spectrum of compound (VIa) showed characteristic bands in the regions 1680 (C═O), 1260 (C—O—C asymmetric) and 1040 cm^{-1} (C—O—C symmetric) while IR spectrum of compound (VIb) showed important bands in the regions 1650 (C═O), 1260 and 1050 cm^{-1} (C—O—C asymmetric and symmetric). The mass spectrum of compound (VIb) exhibited peaks at m/z 444 [M^+], 429, 282, 265, 247, 232, 180, 152, 137 and 124. Compounds (VIa) and (VIb) were than condensed with aromatic aldehydes (VII) in presence of base to afford the resultant chalcones (VIIIa–d) IR spectra of compounds (VIIIa–d) showed peaks at 1630 for carbonyl group and peaks at 1600 and 1500 cm^{-1} were indicative of the presence of benzene nucleus. The CH deformation frequencies characteristic of *trans* ethylenes are found in the regions 1380–1250 and 1000–950 cm^{-1}. Bands in the regions 1260 (C—O—C asymmetric) and 1040 cm^{-1} (C—O—C symmetric) are also observed.

The chalcone (VIIIb) was treated firstly with DMSO and iodine crystal to yield the resultant 7-(2-pentachlorophenoxy ethoxy)-flavone (IXa) which showed characteristic carbonyl frequency at 1630 cm^{-1}. Secondly treatment of chalcone (VIIIb) with bromine in acetic acid afforded the dibromo derivative (X). Finally the reaction of chalcone with alkaline hydrogen peroxide afforded the corresponding 7-(2-pentachlorophenoxy ethoxy)-flavonol (IXb). IR spectrum shows band at 3400 cm^{-1} (—OH). A strong band is observed at 1600 cm^{-1} due to the overlapping of C═O and C═C frequencies.

Antibacterial activity

Compounds (III–VIII) were screened for their antibacterial activity against

Citrobactor spp., K. pneumoniae, P. vulgaris, E. coli, P. aeruginosa, S. coagulase, S. albus and *S. faecalis* by paper disc diffusion method[9] at a conc. of 100 μg/mL using ethanol as solvent. Bis-(pentachlorophenoxy)-ethane (IV) one of the side products during the course of our synthetic reactions is found to be active against *S. albus* and *S. aureus* whereas compound (III) containing one pentachlorophenoxy residue is completely inactive against tested microorganisms. It seems that presence of another pentachlorophenoxy residue in the molecule enhances the activity of the system. Compound (VIb), a pentachlorophenoxy-ethoxy substituted resacetophenone molecule is moderately active against *E. coli* whereas introduction of α, β-unsaturated carbonyl system in this molecule (VIb), considerably enhances the reactivity of compounds (VIIIb–d) against *S. albus* and *S. aureus*. Activity of the compound (Va) against *S. aureus* and *P. aeruginosa* is an indication that *p*-OH group along with —$COCH_3$ in a phenyl ring is an importnat structural feature for activity.

EXPERIMENTAL

Melting points reported are uncorrected. The IR spectra (Nujol) were recorded on Perkin-Elmer 150P spectrophotometer. Mass spectra were recorded at 70 eV. on Jeol D-300 spectrometer. Pentachlorophenol-Koch-Light Laboratories Ltd. sample was used.

2-(Pentachlorophenoxy)-ethyl bromide (III) and 1,2-bis-(pentachlorophenoxy)-ethane (IV)

A mixture of (I) (0.01 mole), 1,2-dibromoethane (0.01 mole) and anhydrous K_2CO_3 (0.01 mole) in acetone (25 mL) was refluxed for 16 h. The completion of the reaction was judged by negative test with alcoholic ferric chloride. After the completion of the reaction the resulting solution was filtered and the residue in the flask was washed with boiling acetone (3 × 10 mL) and again filtered. The filtrate was concentrated and left at room temperature. The separated solid was recrystallised from petroleum ether to give(III) as white needles, (yield 22%), m.p. 74°C. (Calcd: C, 25.72; H, 1.08; $C_8H_4Cl_5OBr$, found: C, 25.27; H, 1.06). IR: 1220 (C—O—C asymmetric), 1020 cm^{-1} (C—O—C symmetric).

The residue obtained after the removal of acetone was treated with dil. HCl and the resulting compound was filtered, washed with water and dried. Recrystallisation from benzene gave (IV) as white globules (yield 29%), m.p. 222°C. (Calcd: C, 30.07; H, 0.72; $C_{14}H_4Cl_{10}O_2$, found: C, 29.65; H, 0.81). IR: 1060–1030 (C—O—C) cm^{-1}.

4-(2-Pentachlorophenoxy ethoxy)-acetophenone (VIa)

A mixture of (III) (0.01 mole), *p*-hydroxyacetophenone (Va) (0.01 mole) and anhydrous K_2CO_3 (0.01 mole) in the DMF was refluxed for 8 h. The reaction mixture was treated with dil. HCl and the solid obtained was filtered, washed with water and recrystallised from benzene-ethanol (80:20 v/v) to give (VIa) as brown needles (yield 20%), m.p. 168°C. (Calcd: C, 44.80; H, 2.56;

$C_{16}H_{11}O_3Cl_5$, found: C, 43.98; H, 2.56). IR: 1680 (C═O), 1260 (C—O—C asymmetric), 1040 cm^{-1} (C—O—C symmetric).

2-Hydroxy-4-(2-pentachlorophenoxy ethoxy)-acetophenone (VIb)

A mixture of (III) (0.01 mole), resacetophenone (Vb) (0.01 mole) and anhy. K_2CO_3 (0.04 mole) in acetone (100 mL) was refluxed for 26 h. Acetone was distilled off and the residue was treated with ice-cold water and dil. HCl. The solid obtained was filtered, washed with water and recrystallised from ethanol to give (VIb) as white needles, (yield 25%), m.pt. 168°C. (Calcd: C, 43.20; H, 2.49; $C_{16}H_{11}O_4Cl_5$, found: C, 42.54; H, 2.47). IR: 1650 (C═O), 1260 (C—O—C asymmetric), 1050 cm^{-1} (C—O—C symmetric). Mass: m/z 444 (M^+), 429, 282, 247, 232, 180, 152, 137 and 124.

4′-(2-Pentachlorophenoxy ethoxy)-Chalcone (VIII a–d)

To a mixture of (VI) (0.005 mole), substituted benzaldehydes (VII) (0.008 mole) in ethanol (100 mL) was added sodium hydroxide (50%, 4 mL) with constant stirring. The reaction mixture was stirred for 6 to 10 h. at room temperature and then refluxed for 2 h. The reaction mixture was cooled and poured over crushed ice and dil. HCl.

The solid obtained was filtered off and recrystallised from the proper solvent to give (VIIIA) as orange plates, (VIIIb) as orange globules, (VIIIc) as orange red globules and (VIIId) as brown globules, respectively.

TABLE-1

Comp.	m.p. (°C)	Yield%	Solvent	Formula	Found/(Calcd.) C	Found/(Calcd.) H
VIIIa	195	20	DMF	$C_{23}H_{15}Cl_5O_3$	53.43 (53.43)	2.80 (2.90)
VIIIb	184	54	acetone	$C_{23}H_{15}O_4Cl_5$	53.50 (51.83)	2.92 (2.81)
VIIIc	136	45	ethanol	$C_{24}H_{17}O_5Cl_5$	50.20 (51.20)	3.05 (3.02)
VIIId	170	60	ethanol	$C_{23}H_{14}O_4Cl_6$	48.07 (48.67)	2.41 (2.46)

IR: 1650–1630 (C═O), 1600–1400 (C═C), 1380–1250 cm^{-1} and 1000–950 cm^{-1} (*trans*-ethylenes).

7-(2-Pentachlorophenoxy ethoxy)-flavone (IXa)

A mixture of (VIIIb) (0.005 mole), DMSO (20 mL) and iodine crystal was refluxed for 30 min and then poured on to cold water. The solid obtained was filtered, washed with 20% aq. sodium thiosuphate and recrystallised from acetone + ethanol (2:1, v/v) to give (IXa) as yellow powder (yield 30%), m.p. 200°C. (Calcd: C, 52.03; H, 2.47; $C_{23}H_{13}O_4Cl_5$, found: C, 50.26; H, 1.39). IR: 1630 (C═O), 1250 (C—O—C asymmetric), 1040 cm^{-1} (C—O—C symmetric).

2′-Hydroxy-4′-(2-pentachlorophenoxy ethoxy)-α, β-dibromo chalcone (X)

Compound (VIIIb) (0.005 mole) was suspended in acetic acid (15 mL) and to this was added a solution of bromine in acetic acid (6.4 mL). The mixture was stirred for 15 min and the solid obtained was filtered, washed with acetic acid and finally with petroleum ether and recrystallised from benzene to give (X) as white powder (yield 80%), m.p. 240°C. (Calcd: C, 39.87; H, 2.18; $C_{23}H_{15}O_4Cl_5Br_2$, found: C, 38.41; H, 0.90). IR: 1630 (C=O), 1250 (C—O—C asymmetric), 1040 cm^{-1} (C—O—C symmetric).

7-(2-Pentachlorophenoxy ethoxy)-flavonol (IXb)

Compound (VIIIb) (0.005 mole) was dissolved in methanol (20 mL). To this solution sodium hydroxide (20%, 10 mL) was added. The reaction mixture was kept at 0°C in ice bath and to this hydrogen peroxide (4 mL) was added with stirring. Further stirring was continued in ice (2 h) and at room temperature (3 h, 20°C). The reaction mixture was acidified with ice cold acetic acid, filtered, washed with water and the solid obtained was recrystallised from acetic acid to give (IXb) as yellow needles, (yield 33%), m.p. 210°C. (Calcd: C, 50.51; H, 2.39; $C_{23}H_{13}O_5Cl_5$, found: C, 49.57; H, 1.63). IR: 3400 (—OH), 1600 (C=C and C=O), 1240 (C—O—C asymmeteric) and 1060 cm^{-1} (C—O—C symmetric).

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