

be distilled easily under high vacuum without decomposition. Compound **4b** was obtained as pale yellow crystals, the others were light-yellow oils. The structure of the compounds synthesized was determined on the basis of their ir and ^1H nmr spectra.

Methoxyphenyl derivatives **4b-d** were demethylated with pyridine hydrochloride to the corresponding phenols **5a-c**. The reaction was carried out by refluxing **4b-d** with an excess of pyridine hydrochloride either without any solvent or in dry quinoline [13,14]. It was found that in quinoline the reaction was running very slow and the overall yield of product **5** was less than 20%. When the demethylation was carried out without solvent, product **5** was obtained in good yield (60-70%) providing the optimal reaction time was 7-12 minutes (see Experimental). When the reaction time was shorter than optimal phenols **5** obtained were admixed with the starting benzofuran. On the other hand, a longer time was found not to be suitable because of the formation of polymers. Crude demethylation products were light yellow precipitates, which formed colorless crystals with sharp melting points after recrystallization from methanol. The structure of the new compounds **5a-c** was confirmed by elemental analysis and characterized by ir and ^1H nmr spectra.

The iodination of **4d** and **5a** led to products iodinated on their phenyl rings, in spite of the methylene protons being activated by the carbonyl group.

When an ethanol solution of 1-[3-(2-butylbenzofuranyl)-2-(4-methoxyphenyl)ethanone (**4d**)] was treated at 60° with iodine in ethanol in the presence of catalytic amounts of sulphuric acid and with the use of perhydrol as an oxidizing agent, the mono iodo derivative **6a** was obtained in 50% yield. Under similar conditions the corresponding hydroxyethanone **5d** gave the diiodo compound **7a** in 34% yield. On the other hand, the reaction of an alkanolic solution of **5d** with iodine in a potassium hydroxide solution gave a mixture of iodinated compounds in the form of an amorphous, alkali-insoluble precipitate. Their ir and ^1H nmr spectra showed that the product mixture contains no hydroxyl group but diiodinated ethers of **5d**. The benzofuranyl methoxy- and hydroxyphenylethanones obtained have been screened for their pharmaceutical, fungicidal, herbicidal, and insecticidal activities. None of the compounds examined showed good pharmaceutical or plant protection activity. Ethyl methoxy **4b** and ethyl hydroxy **5a** showed only weak activity on lemna in laboratory tests.

EXPERIMENTAL

Melting points were determined on a Boetius apparatus and were not corrected. The ir spectra were recorded on a Specord M

80 Carl Zeiss, Jena spectrophotometer. The ^1H nmr spectra were recorded on a TM Bruker DPX 400 spectrometer, in deuteriochloroform as a solvent. Chemical shifts were reported as δ values (ppm) downfield from internal tetramethylsilane. Pyridine hydrochloride was purchased from Merck Chemical Co. Commercial 1,2-dichloroethane was distilled from phosphorus pentoxide before use. Phenylacetyl chloride and *p*-methoxyphenylacetyl chloride were obtained by a standard procedure from the corresponding acids and thionyl chloride as oils, bp [$^\circ\text{C}/\text{mm Hg}$]: 132/12; 150-152/14, **3b**, bp 143/10 lit [15]. Methyl 2-(*o*-formylphenoxy)butanoate, pentanoate and hexanoate were prepared as previously described [11,12].

General Procedure for Synthesis 2-(2-Formylphenoxy)alkanoic Acids **1a-c**.

A mixture of methyl 2-(*o*-formylphenoxy)alkanoates (0.5 mole), potassium hydroxide (39.2 g, 0.7 mole), 350 ml of water and 30 ml of methanol was stirred and heated on a steam bath for 2 hours. The solution was cooled, acidified with 10% hydrochloric acid, and the resulting oil or precipitate was separated. The crude product was dissolved in 5% sodium bicarbonate and then was mixed with activated carbon. The mixture was filtered and next acidified to give crystalline acids.

2-(2-Formylphenoxy)butanoic Acid (**1a**).

This compound was obtained as colorless needles (methyl alcohol), 93.7 g (90%), mp $98-99^\circ$; ir (potassium bromide): ν 1640, 1650 (C=O), 1730 (C=O), 2500-3200 (OH) cm^{-1} ; ^1H nmr: δ 1.13 (t, 3H, CH_3 , $J = 7.4$ Hz), 2.12 (m, 2H, CH_2), 4.78 (t, 1H, CH, $J = 5.7$), 6.90 (d, 1H arom, $J = 7.5$), 7.09 (t, 1H arom, $J = 7.5$), 7.53 (t, 1H arom, $J = 7.0, 1.6$), 7.84 (dd, 1H, arom, $J = 7.0, 1.7$), 10.21 (br s, 1H, COOH), 10.47 (s, 1H, CHO).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{O}_4$ (208.21): C, 63.45; H, 5.81. Found: C, 63.40; H, 5.97.

2-(2-Formylphenoxy)pentanoic Acid (**1b**).

This compound was obtained as pale yellow needles, 96.7 g (87%), mp $79-80^\circ$; ir (potassium bromide): ν 1650, 1660 (C=O), 1730 (C=O), 2500-3200 (OH) cm^{-1} , ^1H nmr (deuteriochloroform): δ 1.00 (t, $J = 7.3$ Hz, 3H, CH_3), 1.58 (m, 2H, CH_2), 2.08 (m, 2H, CH_2), 4.83 (t, $J = 4.9$, 1H, CH), 6.90 (d, $J = 8.4$, 1H arom), 7.10 (t, 1H arom, $J = 7.5$), 7.53 (t, 1H, arom, $J = 7.0, 1.7$) 7.84 (dd, $J = 7.0, 1.7$, 1H arom) 9.49 (br s, COOH), 10.47 (s, CHO).

Anal. Calcd. for $\text{C}_{12}\text{H}_{14}\text{O}_4$ (222.24): C, 64.85; H, 6.35. Found: C, 64.67; H, 6.55.

2-(2-Formylphenoxy)hexanoic Acid (**1c**).

This compound was obtained as colorless crystals, mp $76-78^\circ$; ir and ^1H nmr reported [11].

General Procedure for the Synthesis 2-Alkylbenzofurans **2**.

2-Ethyl and 2-propylbenzofurans were obtained by using the procedure previously described for the preparation of 2-butylbenzofuran [11].

2-Ethylbenzofuran **2a**.

This compound was obtained as a colorless liquid, 62%, bp $69^\circ/5$ mm Hg, lit [9] bp $102^\circ/15$ mm Hg; ^1H nmr: δ 1.20 (t, 3H, CH_3 , $J = 7.5$), 2.55 (q, 2H, CH_2 , $J = 7.4$), 6.26 (s, 1H, furanyl), 7.01-7.50 (m, 4H, phenyl protons).

Anal. Calcd. for $\text{C}_{10}\text{H}_{10}\text{O}$ (146.19): C, 82.16; H, 6.89. Found: C, 82.35; H, 6.98.

2-Propylbenzofuran 2b.

This compound was obtained as colorless liquid, 58%, bp 75-76°/5 mm Hg, lit [9] bp 108-115°/15 mm Hg; ^1H nmr: δ 1.00 (t, 3H, CH_3 , $J = 7.4$), 1.76 (sextet, 2H, CH_2 , $J = 7.4$), 2.73 (t, 2H, CH_2 , $J = 7.4$), 6.36 (s, 1H, furanyl), 7.19 (m, 2H, phenyl), 7.39 (d, 1H, phenyl, $J = 7.5$), 7.46 (d, 1H, phenyl, $J = 6.7$, 1.7).

Anal. Calcd. for $\text{C}_{11}\text{H}_{12}\text{O}$ (160.22): C, 82.46; H, 7.55. Found: C, 82.22; H, 7.70.

General Procedure for the Reaction of 2-Alkylbenzofurans 2a-c with Phenylacetyl Chlorides 3a-b.**Method A.**

To a stirred and cooled (5-10°) solution of 2-alkylbenzofuran (2) (0.1 mole) and phenacetyl chloride 3a (0.1 mole) in dry 1,2-dichloroethane (100 ml), anhydrous tin tetrachloride (24 ml) was added dropwise for forty minutes. After the reaction mixture was stirred for an additional two hours at 5-10°, and cooled to 0°, water (200 ml) was added dropwise. The mixture was stirred for forty minutes. The 1,2-dichloroethane organic phase was separated, washed with water, dried over magnesium sulfate and evaporated to give product 3 as an oil, which was purified either by vacuum distillation or recrystallization from methanol.

Method B.

To a stirred and cooled (5-10°) solution of 2-alkylbenzofuran (1) (0.05 mole) and phenylacetic chloride (2) (0.05 moles) in dry 1,2-dichloroethane (100 ml) anhydrous aluminium chloride (6.6 g, 0.05 mole) was added portionwise for 1 hour and then the reaction mixture was stirred at that temperature for four hours. The mixture was then poured into water (20 ml) with ice (20 g) and hydrochloric acid (7 g). The organic layer was separated, dried and the solvent removed *in vacuo* to leave a brown oil, which was purified by method A.

1-[3-(2-Butylbenzofuranyl)]-2-phenylethanone (4a).

This compound was obtained as a pale yellow oil, yield, method A 65%; method B 60%, bp 174-176°/1 mmHg; ir (carbon tetrachloride): ν 1680 (C=O) cm^{-1} ; uv: ^1H nmr: δ 0.94 (t, 3H, CH_3 , $J = 7.3$), 1.40 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 3.15 (t, 2H, CH_2 , $J = 7.6$), 4.29 (s, 2H, CH_2CO), 7.23-7.36 (m, 7H, arom), 7.47 (m, 1H, arom), 7.96 (m, 1H, arom).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_2$: C, 82.16; H, 6.89. Found: C, 82.04; H, 6.97.

1-[3-(2-Ethylbenzofuranyl)]-2-(4-methoxyphenyl)ethanone (4b).

This compound was obtained from 2a and 3b according to Method A as a dark-yellow oil which was purified by distillation *in vacuo* bp 185-186°/1 mm Hg, next crystallized from hexane giving colorless prisms (57%).

Method B.

Yellow crystals (65%), were obtained which were crystallized from methanol, mp 55-56° ir (carbon tetrachloride): ν CO 1670 cm^{-1} ; ^1H nmr: δ 1.34 (t, $J = 7.5$ Hz, 3H, CH_3), 3.18 (q, $J = 7.5$ Hz, 2H, CH_2), 3.79 (s, 3H, OCH_3), 4.23 (s, 2H, CH_2), 6.88 (dd, $J = 8.4$, 2H, phenyl), 7.17 (dd, $J = 8.4$, 2H, phenyl) 7.33 (m, 2H, benzofuranyl), 7.46 and 7.96 ppm (2m, 2H, benzofuranyl).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_3$ (294.35): C, 77.53; H, 6.16. Found: C, 77.38; H, 6.32.

1-[3-(2-Propylbenzofuranyl)]-2-(4-methoxyphenyl)ethanone (4c).

This compound was obtained from 2b and 3b by Method A in 62% yield and by Method B in 60% yield as a yellow oil, bp 185-188°/1 mm Hg; ir (carbon tetrachloride): ν CO 1680 cm^{-1} ; ^1H nmr: δ 1.01 (t, 3H, CH_3 , $J = 7.4$), 1.79 (sextet, 2H, CH_2 , $J = 7.4$), 3.13 (t, 2H, CH_2 , $J = 7.6$), 3.78 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), 6.88 (d, 2H, phenyl $J = 8.5$), 7.19 (d, 2H, phenyl, $J = 8.4$) 7.31 (m, 2H, benzofuranyl), 7.47 and 7.96 ppm (2m, 2H, benzofuranyl).

Anal. Calcd. for $\text{C}_{20}\text{H}_{20}\text{O}_3$ (308.38): C, 77.90; H, 6.54. Found: C, 77.64; H, 6.72.

1-[3-(2-Butylbenzofuranyl)]-2-(4-methoxyphenyl)ethanone (4d).

This compound was obtained from 2c and 3b by Method A in 67% yield as a pale yellow oil, bp 194-196°/1 mm Hg; ir (carbon tetrachloride): ν CO 1670-1680 cm^{-1} , ^1H nmr: δ 0.94 (t, 3H, CH_3 , $J = 7.4$), 1.40 (m, 2H, CH_2), 1.74 (m, 2H, CH_2), 3.15 (t, 2H, CH_2 , $J = 7.6$), 3.79 (s, 3H, OCH_3), 4.24 (s, 2H, CH_2), 6.88 (d, 2H, phenyl, $J = 8.5$), 7.16 (d, 2H, phenyl, $J = 8.5$), 7.32 (m, 2H, benzofuranyl), 7.47 and 7.96 ppm (2m, 2H, benzofuranyl).

Anal. Calcd. for $\text{C}_{21}\text{H}_{22}\text{O}_3$ (322.40): C, 78.23; H, 6.88. Found: C, 78.20; H, 6.97.

1-[3-(2-Ethylbenzofuranyl)]-2-(4-hydroxyphenyl)ethanone (5a).

A mixture of 4b (2.9 g, 0.01 mole), and pyridine hydrochloride (11.5 g, 0.1 mole) was shaking and heated under reflux for 7-9 minutes. The warm solution was poured into 100 ml of ice water, and mixture was allowed to stand for one hour. The aqueous solution was decanted and the residue dissolved in 20 ml of benzene. The benzene solution was washed with 5% hydrochloric acid, water and extracted twice with 5% sodium hydroxide. Then the alkaline solution was acidified with 5% hydrochloric acid the precipitate was filtered and crystallized from methanol to give colorless needles, 2.2 g (80%), mp 123-124°; ir (chloroform): ν 1670 (C=O), 3300-3400 (OH) cm^{-1} ; ^1H nmr: δ 1.32 (t, $J = 7.5$, 3H, CH_3), 3.19 (q, $J = 7.5$, 2H, CH_2), 4.22 (s, 2H, CH_2), 5.79 (broad s, OH) 6.74 (dd, $J = 8.4$, 2H, phenyl), 7.07 (dd, $J = 8.4$, 2H, phenyl), 7.32 (m, 2H, benzofuranyl), 7.48 and 7.96 (2m, 2H, benzofuranyl).

Anal. Calcd. for $\text{C}_{18}\text{H}_{16}\text{O}_3$ (280.32): C, 77.12; H, 5.75. Found: C, 77.03; H, 5.90.

1-[3-(2-Propylbenzofuranyl)]-2-(4-hydroxyphenyl)ethanone (5b).

In like manner as for 5a, from the reaction of 4c (3.0 g, 0.01 mole) and pyridine hydrochloride (11.5 g, 0.1 mole) for 10 minutes, 5b (2.0 g, 70%) was obtained as white crystals mp 85-86°, after recrystallization from hexane; ir (chloroform): ν 1670 (C=O), 3300-3400 (OH) cm^{-1} ; ^1H nmr: δ 1.02 (t, 3H, CH_3 , $J = 7.4$), 1.76 (sextet, 2H, CH_2 , $J = 7.4$), 3.15 (t, 2H, CH_2 , $J = 7.6$), 4.23 (s, 2H, CH_2), 5.78 (broad s, OH) 6.88 (d, 2H, phenyl $J = 8.5$), 7.18 (d, 2H, phenyl, $J = 8.4$) 7.32 (m, 2H, benzofuranyl), 7.47 and 7.96 ppm (2m, 2H, benzofuranyl).

Anal. Calcd. for $\text{C}_{19}\text{H}_{18}\text{O}_3$ (294.35): C, 77.53; H, 6.16. Found: C, 77.32, H, 6.32.

1-[3-(2-Butylbenzofuranyl)]-2-(4-hydroxyphenyl)ethanone (5c).

This compound was prepared in a similar manner as for 5b from 3.2 g (0.01 mole) of 4d and 11.5 g (0.1 mole) pyridine hydrochloride for 12 minutes. White solid compound 5c had mp 57-58° (2.3 g, 75%); ir (chloroform): ν 1670 (CO), 3300-3350 (OH) cm^{-1} ; ^1H nmr: δ 0.85 (t, $J = 7.5$, 3H, CH_3), 1.32 (m, 2H, CH_2), 1.66 (m, 2H, CH_2), 3.07 (t, $J = 7.6$, 2H, CH_2), 4.14 (s, 2H,

CH₂), 5.77 (broad s, OH), 6.66 ppm (dd, J = 8.4, 2H, phenyl) 6.99 (dd, J = 8.4, 2H, phenyl), 7.24 (m, 2H, benzofuranyl), 7.39 and 7.86 (2m, 2H, benzofuranyl).

Anal. Calcd. for C₂₁H₂₀O₃ (320.39): C, 78.73, H, 6.29. Found: C, 78.60; H, 6.40.

1-[3-(2-Butylbenzofuranyl)]-2-(3-iodo-4-methoxyphenyl)-ethanone **6**.

To a stirred solution of **4d** (1.5 g, 0.005 mole) and iodine (2.5 g, 0.01 mole) in 10 ml of ethanol (15 ml) was added concentrated sulfuric acid (0.4 ml). The solution was heated to 60° and then 30% hydrogen peroxide solution (1.5 ml) was slowly added. Under these conditions, the reaction mixture foamed and precipitation occurred. The reaction mixture was stirred for 1 hour, cooled and a dark brown solid was collected. The solid was crystallized from ethanol to yield 1.1 g (51%), mp 109-110°. ¹H nmr (deuteriochloroform): δ 0.94 (t, J = 7.5, 3H, CH₃), 1.42 (m, 2H, CH₂), 1.76 (m, 2H, CH₂), 3.15 (t, J = 7.5, 2H, CH₂), 3.87 (s, 3H, OCH₃), 4.20 (s, 2H, CH₂CO), 6.80 (d, J = 8.2, 1H, phenyl), 7.20 (dd, J = 8.0, 1H, phenyl), 7.33 (m, 2H, benzofuranyl), 7.49 (m, 1H, benzofuranyl), 7.67 (as, 1H, I-phenyl), 7.93 (m, 1H, benzofuranyl).

Anal. Calcd. for C₂₁H₂₁O₂I (432.30); C, 58.35; H, 4.90; I, 29.36. Found: C, 58.20; H, 5.03; I, 29.15.

1-[3-(2-Ethylbenzofuranyl)]-2-(3,5-diiodo-4-hydroxy)ethanone **7**.

This compound was obtained from **5a** (1.4 g, 0.005 mole) in ethanol (10 ml) by proceeding in the same manner as for **6**, with the exception that an apparatus with large dimensions and a lower temperature (50°) had to be used because the oxidation of hydroiodide by hydrogen peroxide solution is violent. After adding the hydrogen peroxide solution, the mixture was stirred for 15 minutes, cooled and the yellow precipitate was crystallized from ethanol, yield 0.9 g (35%) light beige, mp 178-179°;

¹H nmr (deuteriochloroform): δ 1.37 (t, J = 7.5, 3H, CH₃), 3.20 (q, J = 7.3, 2H, CH₂), 4.16 (s, 2H, CH₂CO), 5.73 (bs, 1H, OH) 7.35 (m, 2H, benzofuranyl), 7.50 (dd, 1H, benzofuranyl), 7.58 (s, 2H, 1-phenyl), 7.90 ppm (dd, 1H, benzofuranyl).

Anal. Calcd. for C₁₉H₁₄O₂I₂ (528.13): C, 43.21; H, 2.67; I, 48.06. Found: C, 43.0; H, 2.82; I, 47.78.

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