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SYNTHESIS AND CONVERSIONS OF 2-CARBETHOXY-3-BROMOMETHYL-7-CHLOROBENZOFURAN

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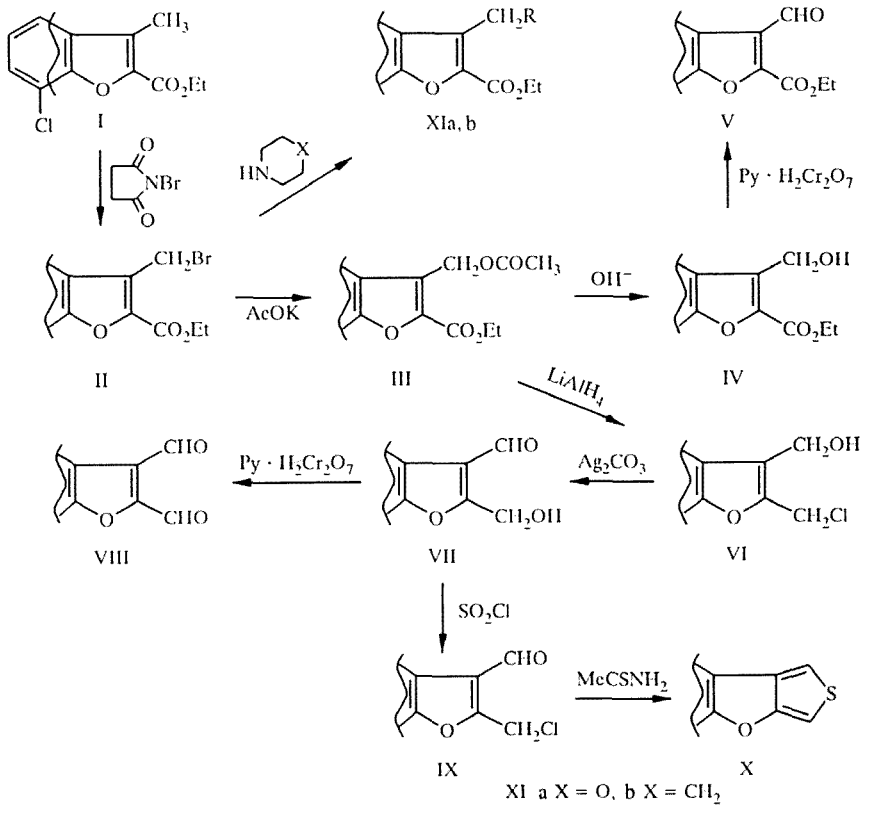
2-Carbethoxy-3-bromomethyl-7-chlorobenzofuran has been synthesized and its conversions studied.

The synthesis and the investigation of the structure of benzofuran derivatives is of interest due to their physiological activity and their use in the preparation of biologically active compounds [1]. It is known that benzofuran derivatives possess antiarrhythmic, antivirus, and other biological activities [2, 3]. By continuing the investigations of benzofuran derivatives [4] we have studied the synthesis of derivatives of 2-carbethoxybenzofuran with a chlorine atom at C(7) of the benzofuran ring, not described in the literature. The initial 2-carbethoxy-3-methyl-7-chlorobenzofuran was obtained from o-chlorophenol by Boheme's method [5]. Bromination of this compound with N-bromosuccinimide gave 2-carbethoxy-3-bromomethyl-7-chlorobenzofuran (II), which by the reaction with potassium acetate was converted to the corresponding 3-acetoxymethyl deri-

Scheme 1



vative (III). Hydrolysis of compound III gave 2-carbethoxy-3-hydroxymethyl-7-chlorobenzofuran (IV), the oxidation of which with pyridine dichromate [6] produced 2-carbethoxy-3-formyl-7-chlorobenzofuran (V). The reaction of compound (III) with lithium alumohydride gave 2,3-dihydroxymethyl-7-chlorobenzofuran (VI), which was then oxidized with Ag_2CO_3 [7] to 2-hydroxymethyl-3-formyl-7-chlorobenzofuran (VII). The latter was converted by the oxidation with pyridine dichromate [6]

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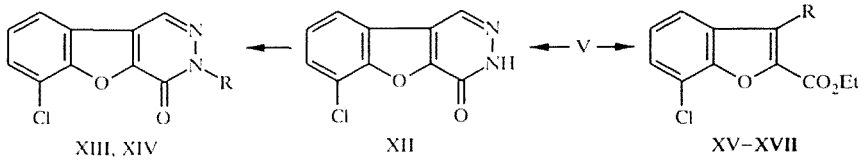
to 2,3-diformyl-7-chlorobenzofuran (VIII). The reaction of compound VII with thionyl chloride led to 2-chloromethyl-3-formyl-7-chlorobenzofuran (IX), which was converted to 5-chlorothieno[3,4-b]benzofuran (X) by the reaction with thioacetamide. In the reaction with morpholine and piperidine compound (II) gives the corresponding 3-aminomethyl derivatives (XIa,b).

Besides this, we achieved cyclization of compound V with hydrazine hydrate, which leads to 3,4-dihydro-6-chloro-4-oxobenzofuro[2,3-d]pyridazine (XII). The latter was converted by treatment with diethyl sulfate to 3,4-dihydro-3-ethyl-6-chloro-4-oxo-benzofuro[2,3-d]pyridazine (XIII) and by treatment with benzyl chloride to the benzyl derivative (XIV). Compound V gave by Knevenagel's reaction [9] with malonic acid 2-carbethoxy-7-chlorobenzofuro-3-acrylic acid (XV), and with diethyl malonate and with malonic acid diamide 2-carbethoxy-chloro-3-(2-dicarbethoxyvinyl)benzofuran (XVI) and 2-carbethoxy-7-chloro-3-(2,2-diaminocarbonylvinyl)benzofuran (XVII) respectively.

Scheme 2



XIII R = CH_3; XIV R = $CH_2C_6H_5$; XV R = —CH=CHCOOH; XVI R = —CH=C(CO_2Et)$_2$; XVII R = —CH=C($CONH_2$)$_2$

EXPERIMENTAL

The ^1H and ^{13}C NMR spectra were taken on a Gemini 200 spectrometer with HMDS as the internal standard. The elemental analysis data for C, H, Cl, and N for the compounds obtained for the first time corresponded to the theoretical values.

2-Carbethoxy-3-bromomethyl-7-chlorobenzofuran (II). A mixture of 11.9 g (0.05 mole) of compound I, 8.9 g (0.05 mole) N-bromosuccinimide, 0.1 g benzoyl peroxide, and 100 ml CCl_4 is refluxed for 4 h. After cooling the precipitate is filtered off and the filtrate evaporated in vacuum. The residue (product) is crystallized from heptane; mp 123-124°C. ^1H NMR spectrum ($CDCl_3$): 7.60-7.10 (3H, m, H_{arom}; 4.85 (2H, s, CH_2); 4.40 (2H, qu, CH_2); 1.38 (3H, t, CH_3). ^{13}C NMR spectrum ($CDCl_3$): 14.26 (CH_3); 20.18 (CH_2); 61.94 (CH_2); 128.15, 124.65, 119.80 (CH_{arom}); 159.19, 150.35, 128.30, 125.50, 117.94, 114.97 (C). Yield 11.1 g (70%).

3-Acetoxymethyl-7-chloro-2-carbethoxybenzofuran (III, $C_{14}H_{13}ClO_5$). A mixture of 9.5 g (0.03 mole) of compound II, 9.8 g (0.11 mole) CH_3COOH, and 120 ml acetic acid is heated for 8 h. The solution is concentrated and treated with 50 ml water. The product is extracted with chloroform, washed with 10% Na_2CO_3 and water, dried over $MgSO_4$, and filtered. The filtrate is evaporated and the residue crystallized from heptane; mp 56-57°C. ^1H NMR spectrum ($CDCl_3$): 7.60-7.10 (3H, m, H_{arom}; 5.40 (2H, qu, CH_2); 4.40 (2H, qu, CH_2); 2.05 (3H, s, OCH_3); 1.35 (3H, t, CH_3). Yield 8.3 g (84%).

2-Carbethoxy-3-hydroxymethyl-7-chlorobenzofuran (IV, $C_{12}H_{11}ClO_4$). A mixture of 4.5 g (0.15 mole) of compound III, 50 ml absolute ethanol, and 1 ml sulfuric acid is left to stand for 12 h at room temperature. The reaction mixture is poured into 50 ml water and the product extracted with ether. The extract is washed with a solution of Na_2CO_3 and water, and dried over $MgSO_4$. The ether is evaporated and the residue crystallized from 70% methanol; mp 69-70°C. ^1H NMR spectrum ($CDCl_3$): 7.65-7.15 (3H, m, H_{arom}); 5.00 (2H, qu, CH_2); 4.40 (2H, qu, CH_2); 2.60 (1H, s, OH); 1.37 (3H, t, CH). Yield 3.7 g (96%).

2-Carbethoxy-3-formyl-7-chlorobenzofuran (V, $C_{12}H_9ClO_4$). A mixture of 2.55 g (0.01 mole) of compound IV and 4.5 g (0.012 mole) of pyridine dichromate in 25 ml methylene chloride is stirred for 6 h at room temperature. The reaction mixture is diluted with 50 ml ether and filtered. The filtrate is passed through a column packed with silica gel and concentrated (by evaporation). The residue is crystallized from heptane; mp 57-58°C. ^1H NMR spectrum ($CDCl_3$): 10.55 (1H, s, CHO); 7.60-7.15 (3H, m, H_{arom}); 4.40 (2H, qu, CH_2); 1.35 (3H, t, CH). Yield 2 g (82%); semicarbazone mp 263-265°C.

2,3-Dihydroxymethyl-7-chlorobenzofuran (VI, $C_{10}H_9ClO_3$). A solution of 1.1 g (0.03 mole) $LiAlH_4$ in 100 ml ether is treated with 3.5 g (0.011 mole) of compound III in 30 ml ether. The mixture is stirrer for 3 h. The excess $LiAlH_4$ is decomposed with water and the product extracted with ether. The solvent is evaporated and the residue crystallized from chloro-

form; mp 143-144°C. ^{1}H NMR spectrum ($CDCl_3$): 760-715 (3H, m, H_{arom}); 4.78 (2H, s, CH_2); 4.70 (2H, s, CH_2). Yield 2 g (85%).

2-Hydroxymethyl-3-formyl-7-chlorobenzofuran (VII, $C_{10}H_7ClO_3$). The boiling mixture of 1.8 g (8 mmole) of compound VI, 30 g of Ag_2CO_3 [7], and 100 ml ethyl acetate is stirred for 24 h. After cooling the precipitate is filtered off and the solvent evaporated. The residue is crystallized from chloroform; mp 123-124°C. ^{1}H NMR spectrum ($CDCL_3$): 10.40 (1H, s, CHO); 7.15-7.70 (3H, m, H_{arom}); 4.80 (2H, s, CH_2). Yield 1.6 g (88%); semicarbazone mp 235-237°C.

2,3-Diformyl-7-chlorobenzofuran (VIII, $C_{10}H_5ClO_3$). A mixture of 1.3 g (6 mmole) of compound VII and 2.9 g (7 mmole) pyridine dichromate in 20 ml dichloroethane is stirred for 10 h at room temperature; 30 ml ether is then added and the mixture filtered. The filtrate is evaporated and the residue crystallized from chloroform; mp 112-113°C. ^{1}H NMR spectrum ($CDCl_3$): 10.35 (1H, s, CHO); 10.45 (1H, s, CHO); 7.70-7.10 (3H, m, H_{arom}). Yield 0.9 g (70%).

2-Chloromethyl-3-formyl-7-chlorobenzofuran (IX, $C_{10}H_6Cl_2O_2$). A solution of 0.75 g (3 mmole) of compound VII in 40 ml ether is treated with 1 ml thionyl chloride. The mixture is left to stand at room temperature for 24 h. The solvent is evaporated and the residue crystallized from petroleum ether; mp 70-71°C. ^{1}H NMR spectrum ($CDCl_3$): 10.40 (1H, s, CHO); 7.15-7.70 (3H, m, H_{arom}); 4.75 (2H, s, CH_2). Yield 0.65 g (79%).

5-Chlorothieno[3,4-b]benzofuran (X, $C_{10}H_5ClOS$). A solution of 0.5 g (2.2 mole) of compound IX and 0.2 g (3 mmole) thioacetamide in 25 ml ethanol is refluxed for 3 h. The solvent is evaporated and the residue crystallized from petroleum ether; mp 243-245°C. Yield 0.2 g (62%).

2-Carbethoxy-3-morpholinomethyl-7-chlorobenzofuran (XIa, $C_{16}H_{18}ClNO_4$). A solution of 1.6 g (5 mmole) of compound II in 25 ml benzene is treated with 0.9 g (10 mmole) morpholine. The reaction mixture is refluxed for 1 h. After cooling the precipitate formed of morpholine hydrobromide is filtered off and the solvent evaporated in vacuum. The product is crystallized from propanol; mp 117-119°C. Yield 1.2 g (72%).

2-Carbethoxy-3-piperidinomethyl-7-chlorobenzofuran (XIb, $C_{17}H_{20}ClNO$) is obtained in the same way from 1.6 g II and 0.7 g piperidine; mp 107-109°C. Yield 1.1 g (70%).

3,4-Dihydro-6-chloro-4-oxobenzofuro[2,3-d]pyridazine (XII, $C_{10}H_5ClN_2O_2$). A solution of 2.5 g (0.01 mole) of compound V and 8 g hydrazine hydrate in 50 ml absolute ethanol is refluxed for 3 h. The solvent is evaporated and the residue treated with 25 ml of a 10% NaOH solution. The mixture obtained is filtered and neutralized with conc. HCl. The precipitate formed is filtered off, washed with water, and crystallized from propanol; mp 267-269°C. ^{1}H NMR spectrum (DMSO-d_6): 11.25 (1H, s, NH); 8.40-7.40 (4H, m, H_{arom}); 2.85 (2H, qu, CH_2); 1.37 (3H, t, CH_3). Yield 1.2 g (40%).

3,4-Dihydro-3-ethyl-6-chloro-4-oxobenzofuro[2,3-d]pyridazine (XIII, $C_{12}H_9ClN_2O_2$). A mixture of 1.1 g (5 mmole) of compound XII and 0.7 g (10 mmole) sodium ethylate in 50 ml absolute ethanol is refluxed for 0.5 h; 1.2 g (8 mmole) of diethyl sulfate is then added and the mixture refluxed for 2 h. The solution is concentrated and the residue crystallized from acetone; mp 211-213°C. ^{1}H NMR spectrum (acetone-D_6): 8.40-7.40 (4H, m, H_{arom}); 3.95 (2H, qu, CH_2); 1.35 (3H, t, CH_3). Yield 0.7 g (63%).

3-Benzyl-3,4-dihydro-6-chloro-4-oxobenzofuro[2,3-d]pyridazine (XIV, $C_7H_{11}ClN_2O_2$). Obtained in the same way as the derivative XIII from 5 mmole of compound XII, 6 mmoles sodium ethylate, and 5 mmole benzyl chloride; mp 233-235°C. ^{1}H NMR spectrum ($CDCl_3$): 8.45-7.40 (9H, m, H_{arom}); 5.10 (2H, s, CH_2). Yield 0.9 g (57%).

2-Carbethoxy-7-chlorobenzofuro-3-acrylic Acid (XV, $C_{14}H_{11}ClO_5$). A mixture of 2.5 g (0.01 mole) of compound V, 1.1 g (0.01 mole) malonic acid, 25 ml pyridine, and 0.5 ml piperidine is refluxed for 8 h. The reaction mixture is poured into 50 ml water and acidified with conc. HCl. The precipitate formed is filtered off, washed with water, and crystallized from propanol; mp 143-145°C. ^{1}H NMR spectrum ($CDCl_3$): 8.27 (1H, d, CH); 7.40-7.15 (3H, m, H_{arom}); 6.20 (1H, d, CH); 4.49 (2H, qu, CH_2); 1.38 (3H, t, CH_3). Yield 1.8 g (62%).

2-Carbethoxy-7-chloro-3-(2,2-dicarbethyvinyl)benzofuran (XVI). A mixture of 2.5 g (0.01 mole) of compound V, 1.6 g (0.01 mole) of diethyl malonate, 0.5 ml piperidine, and 100 ml anhydrous benzene is refluxed with a Dean and Stark attachment until the liberation of water has stopped. The reaction mixture is poured into 50 ml water and acidified with conc. HCl to pH 2; the organic layer is washed with water and dried. The benzene is evaporated and the residue crystallized from methanol; mp 79-80°C. ^{1}H NMR spectrum ($CDCl_3$): 7.40-7.20 (3H, m, H_{arom}); 4.45 (2H, qu, CH_2); 4.10 (2H, qu, CH_2); 3.60 (1H, d, CH); 1.44 (3H, t, CH_3); 1.14 (3H, t, CH_3). Yield 2.7 g (70%).

2-Carbethoxy-7-chloro-3-(2,2-diaminocarbonylvinyl)benzofuran (XVII, $C_{15}H_{13}ClN_2O_5$). A mixture of 1.2 g (5 mmole) of compound V, 0.7 g (6.3 mmole) malonic acid diamide, 20 ml pyridine, and 0.5 ml piperidine is refluxed. The reaction product is treated with 50 ml water and acidified with concentrated HCl. The precipitate formed is filtered off and

crystallized from heptane; mp 235-238°C. ^{13}C NMR spectrum (DMSO-d_6): 169.32, 165.71, 159.44, 141.15, 133.02, 129.76, 128.72, 125.29 (C); 134.21, 129.23, 122.61 (CH, H_{arom}); 112.17 (CH); 61.01 (CH_2); 14.17 (CH_3). Yield 1.1 g (65%).

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